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EDGEWOOD ARSENAL
TECHNICAL REPORT

EATR 4446

OCULAR, CUTANEOUS, RESPIRATORY AND INTRATRACHEAL TOXICITY OF SOLUTIONS OF CS AND EA 3547 IN GLYCOL AND GLYCOL ETHER IN ANIMALS (U)

by

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J. S. Olson

October 1970

DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010

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(U) FOREWORD

The work described in this report was authorized under Task 1B562602AD1302, Riot Control and Chemical Training Systems, Biomedical Evaluation of Riot Control Agents. The work was started in February and completed in September 1969. The experimental data are contained in notebooks MN 2195 and MN 2277.

In conducting the research described in this report, the investigator(s) adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences - National Research Council.

(C) DIGEST

(C) The studies described in this report were performed to assess the toxicities of *o*-chlorobenzylidene malononitrile (CS) and dibenz(b,f)-1,4-oxazepine (EA 3547) in glycol and glycol ether solutions when administered to animals as follows.

1. Single and repeated doses in the eye.
2. Single and repeated doses on the skin.
3. Single and repeated doses applied to cloth on skin.
4. Single doses administered into the trachea.
5. Sprays of the solutions disseminated from the XM30 onto the eyes and skin.
6. Inhalation of aerosols.

(U) The only residual damage that occurred when 1% CS in dipropylene glycol was applied to the skin and eyes of rabbits and monkeys was in the corneas of rabbits that received the repeated doses (5 consecutive days). No residual damage was seen when 1% EA 3547 in dipropylene glycol and in propylene glycol was applied to the skin and eyes of rabbits and monkeys once or for five consecutive days. The same was true of 1% EA 3547 in diethylene glycol monomethyl ether in rabbits. When solutions of 1% CS in dipropylene glycol and 1% EA 3547 in propylene glycol, dipropylene glycol, or diethylene glycol monoethyl ether were administered intratracheally to dogs, no residual damage occurred. Rats and guinea pigs exposed to aerosols of 1% CS in dipropylene glycol, 1% EA 3547 in propylene glycol, and 1% EA 3547 in dipropylene glycol showed no residual pathological effects.

(U) CONTENTS

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(C) OCULAR, CUTANEOUS, RESPIRATORY, AND INTRATRACHEAL TOXICITY OF SOLUTIONS OF CS AND EA 3547 IN GLYCOL AND GLYCOL ETHER IN ANIMALS (U)

I. (C) INTRODUCTION.

(U) The studies described in this report constitute the third phase of a toxicological research program in support of the development of a safe, potent, riot control spray formulation. This research was funded and authorized under the XM30 CS Liquid Fill (ENSURE 269) Program. Phases one and two of this effort* involved the assessment of (1) commercial formulations (the fills of the Chemical MACE MKIV and the Federal Streamer No. 280) and 1% CS in trioctyl phosphate (the fill for the XM32 dispenser) and (2) CS slurries in water containing a wetting agent (the fill for the XM30 dispenser).

(C) Phase three was the screening and testing of candidate solvents in combination with *o*-chlorobenzylidene malononitrile (CS) and dibenz(b,f)-1,4-oxazepine (EA 3547). The purpose was to obtain a riot control spray formulation having the following characteristics.

a. Agent in solution, not a slurry.

b. Causes no permanent eye or skin damage.

c. Causes no damage to the respiratory system if aspirated.

d. Low order of systemic toxicity when absorbed through the skin, eyes, or respiratory system.

e. Chemically stable at ambient or elevated temperatures.

f. Capable of being disseminated from available hardware.

g. Effective against motivated rioters.

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*(U)Weimer, J. T., Owens, E. J., Ballard, T. A., Ferrell, J. F., Everts, J. S., Averill, H. P., and McNamara, B. P. EATR 4301. Toxicity of O-Chlorobenzylidene Malononitrile (CS) in Trioctylphosphate (TOF) Solutions. April 1969. UNCLASSIFIED Report.

Owens, E. J., Ferrell, J. F., Weimer, J. T., Ballard, T. A., Merkey, R. P., Olson, J. S., and Samuel, J. B. EATR 4379. Ocular, Cutaneous, and Intratracheal Toxicity of CS Water Slurries With and Without a Surfactant in Animals. December 1969. UNCLASSIFIED Report.

Weimer, J. T., Ballard, T. A., Merkey, R. P., Olson, J. S., Ferrell, J. F., Everts, J. S., and Owens, E. J. EATR (In publication). Biological Assessment of MK IV Chemical Mace. FOUO Report.

Weimer, J. T., Ballard, T. A., Merkey, R. P., Olson, J. S., Ferrell, J. F., Everts, J. S., and Owens, E. J. EATR (In publication). Biological Assessment of Federal Streamer No. 280. FOUO Report.

(C) A total of 35 agent solvent systems were reviewed for applicability. Of these, the four found to have most of the desired characteristics were 1% CS in dipropylene glycol and 1% EA 3547 in propylene glycol, dipropylene glycol, and diethylene glycol monomethyl ether. This is a report of the secondary toxicity testing and chemical stability studies that were performed on these solutions to evaluate the action of:

a. Single and repeated doses on the eye.

b. Single and repeated doses on the skin

c. Single doses administered into the trachea.

d. Single and repeated doses applied to cloth on skin.

e. Sprays of the solutions disseminated from the XM30 onto the eyes and skin.

f. Temperature effects on dissemination characteristics and stability of solutions.

(U) Some information on the toxicities of propylene glycol, dipropylene glycol, diethylene glycol monomethyl ether, CS, and EA 3547 is contained in appendix A.

II. (C) MATERIALS AND EXPERIMENTATION.

A. (C) Materials.

1. (U) Solvents.

Propylene glycol, U.S.P. Lot 781046, Fisher Chemical Co.

Dipropylene glycol, practical, Lot P 4773, Eastman Organic Chemical Company.

Diethylene glycol monomethyl ether, purified, Lot 77186, Fisher Chemical Company.

2. (C) Agents.

CS, Lot 2011-73-1003, Fisher Chemical Company.

EA 3547 (T2806), no lot number, received from Suffield Experimental Station, Canada, in 1962.

3. (U) Formulations.

The formulations tested were:

1% CS in dipropylene glycol
1% EA 3547 in propylene glycol
1% EA 3547 in dipropylene glycol
1% EA 3547 in diethylene glycol monomethyl ether

All but the last formulation were tested by every route of administration. Inhalation testing in rodents and ocular and cutaneous studies in primates were not performed with 1% EA 3547 in diethylene glycol monomethyl ether after studies with rabbits showed it to be more hazardous than the other two solvents. The percutaneous LD50 of diethylene glycol monomethyl ether is about equal to that of trioctylphosphate or about 20 gm/kg in the clipped rabbit. Neither propylene nor dipropylene glycol is absorbed appreciably by the skin nor have they been shown to be systemically toxic by this route of administration.

4. (U) Stability and Viscosity of Solutions.

Appendix B contains a description of viscosity and stability studies performed with 1% CS and 1% EA 3547 in propylene glycol, dipropylene glycol, and diethylene glycol monomethyl ether. It was shown that four of the six solutions were stable over a 30-day period when stored at 75° and 140°F. The unstable solutions were 1% CS in propylene glycol and diethylene glycol monomethyl ether. Aside from a preliminary screen for eye and skin effects (not included in this report), no other toxicity studies were performed with these two solutions. It was also shown that the pour points of both propylene and dipropylene glycol are below -50°F. A 1% EA 3547 solution in propylene or dipropylene glycol is slightly less viscous than the solvent alone. The same is true for a 1% CS solution in dipropylene glycol. The viscosities of 1% EA 3547 and 1% CS in dipropylene glycol are almost the same, within experimental error.

5. (U) Animals.

The animals used in these studies and their approximate weights were as follows:

New Zealand albino rabbits, 2 kg
Rhesus monkeys, 2 to 3 kg
Registerable beagle dogs, 10 kg
Hartley strain albino guinea pigs, 200 gm
Sprague-Dawley rats, Wistar strain, 150 gm

B. (U) Experimentation.

1. General Procedures.

a. Ocular Administration.

Prior to dosing, both eyes of each animal were examined, and any animals with eye defects or irritation were eliminated. Prior to and throughout the observation period, the animals were individually caged in raised pens that were free from animal bedding and were above droppings.

One day after exposure, all dosed eyes were flushed with isotonic saline and wiped with surgical gauze. Clinical observations of the dosed and undosed eyes were then recorded. Following this, one drop of fluorescein sodium ophthalmic solution U.S.P. was instilled into each eye, and the eyes were flushed with saline. Corneal damage was then assessed by examining the eye under ultraviolet light. Two days after exposure and after clinical observations had been recorded, all dosed eyes were flushed with isotonic saline and treated with one drop of 15% sodium sulfacetamide ophthalmic solution, modified. On subsequent days, only those eyes that

[illegible] treatment was flushed, cleaned, and treated with ophthalmic solution. Testing for corneal involvement with [illegible] sodium was conducted when damage was suspected.

The evaluation of ocular irritation was done in accordance with the modified Draize technique described in the "Illustrated Guide for Grading Eye Irritation by Hazardous Substances" published by the US Food and Drug Administration. Each animal was observed for redness of the conjunctiva, chemosis, iritis, and corneal involvement. The grades for ocular lesions are shown in table I.

b. Cutaneous Administration.

The animals were prepared by clipping the hair off the back. Any animals with skin abnormalities (abrasions, discoloration, etc.) were excluded. After dosing, no subsequent treating was done other than reclipping the hair to observe skin reactions. The evaluation of skin irritation was done by the grading system shown in table II.

2. Specific Procedures.

a. Single-Dose Ocular and Cutaneous Tests.

Six rabbits and five monkeys (in one instance, six monkeys) per formulation received ocular doses of 0.2 ml and cutaneous doses of 1.0 ml. Four control rabbits and two monkeys per solvent received ocular doses of 0.2 ml and cutaneous doses of 1.0 ml.

Ocular dosing was accomplished by holding the animal firmly but gently until quiet. The test material was placed in the right eye by gently pulling the lower lid away from the eyeball to form a cup into which the test material was dropped. The lids were then gently held together for 1 second.

Cutaneous testing was accomplished by holding the animal firmly but gently and applying the test material to the clipped back.

The animals were observed for ocular and cutaneous irritation for 4 hours after dosing and daily for 30 days. Necropsies were performed on two agent-dosed and two control animals per formulation 3 and 30 days after dosing.

b. Repeated-Dose Ocular and Cutaneous Tests.

Two groups of six rabbits per formulation received ocular doses of 0.2 and 0.05 ml, respectively, and cutaneous doses of 1.0 and 0.2 ml, respectively, daily for 5 days. Five monkeys per formulation received only the higher ocular and cutaneous doses. Techniques were the same as those used for single dosing.

Two groups of four control rabbits per formulation received ocular doses of 0.2 and 0.05 and cutaneous doses of 1.0 ml and 0.2 ml, respectively, of the appropriate solvent daily for 5 days. Two monkeys per solvent received the 0.2-ml ocular and 1.0-ml cutaneous doses for 5 days.

Table I (U). Gradations of Eye Effects

Effect	Grade*
Cornea:	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible	[1]
Easily discernible translucent areas, details of iris slightly obscured	2
Nacreous areas, no details of iris visible, size of pupil barely discernible	3
Complete corneal opacity, iris not discernible	4
Iris:	
Normal	0
Markedly deepened folds, congestion, swelling, moderate circumcorneal injection (any of these or combination of any thereof), iris still reacting to light (sluggish reaction is positive)	[1]
No reaction to light, hemorrhage, gross destruction (any or all of these)	2
Conjunctivae:	
Redness (refers to palpebral and bulbar conjunctivae excluding cornea and iris):	
Vessels normal	0
Some vessels definitely injected	1
Diffuse, crimson red, individual vessels not easily discernible	[2]
Diffuse beefy red	3
Chemosis:	
No swelling	0
Any swelling above normal (includes nictitating membrane)	1
Obvious swelling with partial eversion of lids	[2]
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

*Bracketed figures indicate lowest grades considered positive under Section 191.12 of the Federal Hazardous Substances Labeling Act Regulations.

Table II (U). Gradations of Skin Effects

Effect	Grade
Erythema	
No erythema	0
Mild erythema	1
Moderate erythema	2
Severe erythema	3
Erythema with edema	4
Necrosis:	
No necrotic tissue	0
Less than 50% necrotic tissue	1
50%-100% necrotic tissue	2
100% necrotic tissue with well-defined eschar formation	3
Dehydration and/or desquamation:	
No dehydration or desquamation	0
Mild dehydration or desquamation	1
Moderate dehydration or desquamation	2
Severe dehydration or desquamation	3

The animals were examined for ocular and cutaneous irritation prior to each daily dosing. Daily observations were made for 30 days after administration of the last dose. Necropsies were performed on two agent-dosed and two control rabbits per dose of each formulation 3 and 30 days after the last dosing.

c. Single-Dose Patch Tests.

Six rabbits per formulation received a dose of 1.0 ml applied to sateen patches taped to their clipped backs. Four control rabbits per formulation received a dose of 1.0 ml of the solvent applied to sateen patches taped to their clipped backs. The patches were removed in 24 hours and the rabbits' backs were examined for cutaneous irritation daily for 30 days. Necropsies were performed on two agent-dosed and two control rabbits per formulation 3 and 30 days after dosing.

d. Repeated-Dose Patch Tests.

Two groups of six rabbits per formulation received doses of 1.0 and 0.2 ml applied to sateen patches taped to their clipped backs daily for 5 days. Two groups of four control rabbits per formulation received doses of 1.0 ml and 0.2 ml of the solvent in the same manner. On the sixth day, the patches were removed from all rabbits, and each rabbit's back was then examined for cutaneous irritation daily for 30 days. Areas of irritation caused by the masking tape were

not considered in scoring. Necropsies were performed on two agent-dosed and two control rabbits per dose per formulation 3 and 30 days after removal of the patches.

e. Ocular Application by Spraying.

The rabbits were sprayed in an outdoor test area where the ambient temperature was 60°F and the relative humidity was 60%. Each rabbit spent less than 5 minutes out-of-doors and then was returned to the observation room where the temperature was 70°F and the relative humidity, 48%.

Each formulation was loaded into an XM30 spray device that was pressurized with a nitrogen cylinder. The device was shaken vigorously before each animal test. Two groups of six rabbits per formulation were restrained in boxes which allowed only their heads to protrude. Each formulation was sprayed from a distance of 5 feet toward the right eyes of six rabbits for 1 second or 5 seconds, respectively. The left eye of each rabbit served as a control. The eyes were examined for signs of ocular irritation for 4 hours after dosing and daily for 30 days after dosing. Necropsies were performed on two rabbits from each group 3 and 30 days after dosing.

f. Intratracheal Administration.

Beagle dogs ranging in age from 9 months to 4 years were examined by a veterinarian prior to dosing and judged to be clinically free of upper respiratory tract infections. The dogs were then anesthetized intravenously with sodium methohexital at a dose of 5 mg/kg of body weight. By use of a laryngoscope, the dogs were intubated; and the test formulations or solvents were deposited in the upper 2 inches of the trachea. Four dogs per formulation received 0.5 ml and two control dogs per formulation received 0.5 ml of the solvent.

The dogs were observed daily for the first week after dosing and twice a week for the remainder of the 30-day observation period. Necropsies were performed on two agent-dosed and one control dog per formulation 3 and 30 days after dosing.

g. Inhalation Exposures.

Inhalation testing of pneumatically generated aerosols of 1% CS in dipropylene glycol and 1% EA 3547 in propylene glycol and dipropylene glycol was conducted in accordance with Research Laboratories SOP No. 70-3.* Twenty-two rats and 22 guinea pigs were exposed to a Ct** of about 2000 mg-min/cu m of each agent for 2 minutes. Control groups of 10 rats and 10 guinea pigs were exposed to aerosols of the solvents for 2 minutes. The exposed animals and the controls were observed for 30 days after exposure, and toxic signs were recorded. Three and 30 days after exposure, three animals from each group were necropsied.

*(U) RL SOP 70-3. The Search for and Selection of Toxic Chemical Agents for Weapons Systems. 1 June 1967. UNCLASSIFIED Document.

**Ct = concentration of agent X time (minutes).

h. Temperature and Humidity.

During dosing and throughout the observation periods, ambient temperatures ranged from 65° to 75°F, and relative humidities ranged from 40% to 80%.

III. (U) RESULTS.

In none of these studies did any animal display signs of systemic toxicity. Only one group of control animals showed any signs, and these are described below. (All tables are contained in appendix C.)

A. Ocular and Cutaneous Testing (Single Dose).

1. EA 3547 (1% in Diethylene Glycol Monomethyl Ether) in Rabbits.

An ocular dose of 0.2 ml of this formulation produced a mild redness at the periphery of the eyelids of the six rabbits for 5 to 15 minutes. The only other effect observed was mild chemosis, which occurred in two of the rabbits in 1 day and persisted less than 24 hours. The only sign produced by a cutaneous dose of 1.0 ml of this formulation was mild erythema in two of the six rabbits within 1 day. This condition persisted for 3 days.

2. EA 3547 (1% in Propylene Glycol).

a. Rabbits.

The only sign produced by an ocular dose of 0.2 ml of this formulation was a mild redness at the periphery of the eyelids of the six rabbits. This condition persisted 5 to 15 minutes. A cutaneous does of 1.0 ml of this formulation produced no visible signs of skin irritation in the six rabbits at any time during the 30-day observation period.

b. Monkeys.

The only sign that resulted from an ocular dose of 0.2 ml of this formulation was an immediate redness of the conjunctivae in all five monkeys which persisted for 5 to 15 minutes. A cutaneous dose of 10 ml produced no visible signs of skin irritation during the 30-day period.

3. EA 3547 (1% in Dipropylene Glycol).

a. Rabbits.

The only sign produced by an ocular dose of 0.2 ml of this formulation was a mild redness at the periphery of the eyelids of the six rabbits, which persisted for 15 minutes. A cutaneous dose of 1.0 ml produced no visible signs of skin irritation during the 30-day observation period.

b. Monkeys.

An ocular dose of 0.2 ml of this formulation produced an immediate redness of the conjunctivae in all five monkeys which persisted for 5 to 15 minutes. No other signs of irritation were observed. A cutaneous dose of 1.0 ml of this formulation produced no signs of irritation.

4. CS (1% in Dipropylene Glycol).

a. Rabbits.

An ocular dose of 0.2 ml of this formulation produced an immediate mild redness of the conjunctivae and, within 24 hours, moderate chemosis in all the rabbits. The animals did not open their dosed eyes for 30 to 45 minutes after application of the solution. Conjunctival redness and swelling persisted for 1 to 3 days; no additional signs appeared (table C-I).

A cutaneous dose of 1.0 ml of this formulation produced mild to moderate erythema in five of the six rabbits in 1 day. This condition persisted for 1 to 3 days. The rabbits' skins appeared normal throughout the remainder of the 30-day observation period (table C-II).

b. Monkeys.

An ocular dose of 0.2 ml of this formulation produced an immediate redness of the conjunctivae in six monkeys. This condition persisted for less than 1 hour in all but one of the monkeys. In that animal, redness and a transient mild chemosis persisted for 3 days. No subsequent signs of ocular irritation were observed. A cutaneous dose of 1.0 ml of this formulation produced no signs of irritation.

B. Ocular and Cutaneous Testing (Repeated Doses).

1. EA 3547 (1% in Diethylene Glycol Monomethyl Ether) in Rabbits.

An ocular dose of 0.2 ml of this formulation applied daily for 5 days immediately produced a mild redness at the periphery of the eyelids in all rabbits and persisted up to 15 minutes after each application. Two of the six rabbits displayed mild chemosis, one on the first day and the other on the third day; but this sign lasted only 1 day. The same two rabbits had a mild redness of the conjunctivae on the first day which persisted for 2 to 3 days and recurred in one rabbit for only 1 day after the last dose. One other rabbit displayed a mild conjunctival redness after the first dose, which persisted for 1 day. The remaining three rabbits displayed no signs of ocular irritation other than the initial response (table C-III). The only sign produced by repeated ocular doses of 0.05 ml was a slight momentary redness of the eyelids immediately after each application.

Repeated cutaneous doses of 1.0 ml of this formulation produced mild to moderate erythema in four rabbits 1 day after the first dose. One additional rabbit displayed mild erythema the day after the fifth dose. In each instance the erythema disappeared for several days and then recurred. No signs were present after the seventh day (table C-IV). A cutaneous dose of 0.2 ml applied daily for 5 days produced no visible signs of irritation throughout the dosing period and the 30-day observation period.

2. EA 3547 (1% in Propylene Glycol).

a. Rabbits.

Ocular doses of 0.2 and 0.05 ml of this formulation administered daily for 5 days to two groups of six rabbits produced only a momentary mild redness at the periphery of the

eyelids upon daily application. Repeated cutaneous doses of 1.0 and 0.2 ml on two groups of six rabbits produced no signs of irritation during the 30-day observation period.

b. Monkeys.

An ocular dose of 0.2 ml of this formulation administered daily for 5 days to five monkeys produced only an immediate redness of the conjunctivae after each application, which persisted for 5 to 15 minutes. A repeated cutaneous dose of 1.0 ml administered to five monkeys produced no signs of irritation during the dosing period or the subsequent 30-day observation period.

3. EA 3547 (1% in Dipropylene Glycol).

a. Rabbits.

Ocular doses of 0.2 and 0.05 ml of this formulation administered daily for 5 days to two groups of six rabbits produced only a momentary redness at the periphery of the eyelids upon each application.

One rabbit given repeated cutaneous doses of 1.0 ml had no signs. The other five had transient mild erythema over a period of 1 to 6 days. No signs of cutaneous irritation were observed in the subsequent observation period (table C-V). Cutaneous doses of 0.2 ml of this formulation produced mild erythema in three rabbits, initially appearing on the day after the first to fourth dose and lasting 1 to 2 days. One rabbit had moderate erythema for 2 days after the second dose. The remaining two rabbits showed no signs of cutaneous irritation (table C-V).

b. Monkeys.

The only sign produced by an ocular dose of 0.2 ml of this formulation administered daily for 5 days to five monkeys was an immediate redness of the conjunctivae after each application, which persisted for 5 to 15 minutes. A cutaneous dose of 1.0 ml of this formulation on five monkeys produced no signs of cutaneous irritation during the 5-day dosing period or the subsequent 30-day observation period.

4. CS (1% in Dipropylene Glycol).

a. Rabbits.

Repeated ocular doses of 0.2 ml of this formulation produced immediate redness of the conjunctivae. Mild to severe chemosis, mild to moderate redness of the conjunctivae, and mild to moderate iritis occurred the day after the first dose. Iritis persisted for 3 days. Severe chemosis persisted for 2 weeks at which time the eyelids became ptotic. Ptosis persisted for another week. Corneal ulcerations were noted the day after the fourth dose and they persisted in all six rabbits until the animals were killed for necropsy 3, 21, and 30 days after administration of the fifth dose (table C-VI).

Ocular doses of 0.05 ml produced immediate conjunctival redness. The day after administration of the first dose, redness was still apparent; five of the rabbits had mild to moderate chemosis; and four had mild to moderate iritis. Conjunctival redness persisted for 6 to

10 days. Chemosis progressed to the severe stage in four rabbits during the dosing period and persisted for 7 to 10 days. Iritis persisted 2 to 3 days. Corneal ulcerations occurred in four of the rabbits in 3 to 4 days after the first dose and persisted up to 7 days (table C-VI).

Daily cutaneous doses of 1.0 ml produced mild to severe erythema in all rabbits in 1 to 4 days. This condition persisted up to 8 days. Mild necrosis appeared in 13 days in two of the remaining four rabbits and persisted for 4 days (table C-VII).

A cutaneous dose of 0.2 ml produced mild erythema in all rabbits on the day after the first dose. Transient erythema recurred on subsequent dosing. Five of the rabbits displayed mild to moderate erythema the day after administration of the fifth dose. The condition persisted up to 6 days. One of the remaining four rabbits displayed mild necrosis on the 11th day, which persisted for 3 days (table C-VII).

b. Monkeys.

An ocular dose of 0.2 ml of this formulation produced an immediate conjunctival redness after each application. This condition persisted for 30 minutes. Mild to severe chemosis developed in four of the six monkeys the day after administration of the first or second doses. This condition persisted 4 to 6 days. A moderate redness of the conjunctivae persisted in one monkey for 3 days after administration of the second dose. None of the monkeys displayed any signs of ocular irritation from 7 through 30 days (table C-VIII).

An ocular dose of 0.05 ml produced an immediate conjunctival redness after each application. This condition persisted for 15 to 30 minutes. Mild chemosis occurred in four of the monkeys the day after administration of the second dose and persisted 4 to 5 days. Conjunctival redness persisted for 5 days in one of the monkeys. None of the monkeys displayed any signs of ocular irritation from 7 through 30 days (table C-VIII).

Daily cutaneous doses of 1.0 and 0.2 ml of this formulation produced no signs of cutaneous irritation during the dosing period or in the 30-day observation period following the fifth dose.

C. Single-Dose Patch Tests in Rabbits.

1. EA 3547 (1% in Diethylene Glycol Monoethyl Ether).

A single cutaneous dose of 1.0 ml of this formulation applied to sateen patches taped to the clipped backs of six rabbits produced mild to moderate erythema in 24 hours, which persisted for 1 day in all rabbits. No cutaneous irritation was observed in the subsequent 30-day observation period.

2. EA 3547 (1% in Propylene Glycol).

Patch tests with 1.0 ml of this formulation produced no signs of cutaneous irritation in the 30-day observation period.

3. EA 3547 (1% in Dipropylene Glycol).

Patch tests with 1.0 ml of this formulation produced mild erythema in one rabbit and moderate erythema in another, appearing the first day after application and disappearing the next day. No other cutaneous responses were observed in the subsequent 30 days.

A single cutaneous dose of 1.0 ml of dipropylene glycol applied to the sateen patches of four control rabbits produced mild erythema in 1 day, which disappeared by the next day. No other signs were observed in the subsequent 30 days.

4. CS (1% in Dipropylene Glycol).

Patch tests with 1.0 ml of this formulation produced no signs of irritation to the four rabbits during the 30-day observation period.

D. Repeated-Dose Patch Tests in Rabbits.

1. EA 3547 (1% in Diethylene Glycol Monomethyl Ether).

Cutaneous doses of 1.0 and 0.2 ml of this formulation applied daily for 5 days to sateen patches taped to the clipped backs of six rabbits per dose produced no signs of irritation during the 30-day observation period.

2. EA 3547 (1% in Propylene Glycol).

Repeated application of 1.0 and 0.2 ml of this formulation to patches on six rabbits per dose produced no signs of cutaneous irritation during the 30-day observation period.

3. EA 3547 (1% in Dipropylene Glycol).

A cutaneous dose of 1.0 ml of this formulation applied repeatedly to six rabbits produced mild erythema in two rabbits for 1 day -the day after application of the fifth dose. No other cutaneous irritation occurred during the observation period (table C-IX). The 0.2-ml doses produced mild to moderate erythema in three of six rabbits 1 or 2 days after application of the fifth dose and persisted for 1 day. No other signs of cutaneous irritation occurred during the subsequent observation period (table C-IX).

4. CS (1% in Dipropylene Glycol).

When 1.0 ml of this formulation was applied to the patches for 5 days, mild to moderate erythema appeared in all rabbits 1 to 2 days after the fifth dose. This condition persisted for 2 or 3 days. On the fourth day, a mild necrosis developed; it persisted 2 days in two rabbits, 7 days in one, and 9 days in the other (table C-X).

A cutaneous dose of 0.2 ml of this formulation applied in the same manner produced mild to moderate erythema in four rabbits the day after administration of the fifth dose, and this condition persisted up to 3 days. Two rabbits developed a mild necrosis on the fourth day after removal of the patch; it persisted 2 days (table C-X).

E. Spray Tests, Rabbits.*

1. EA 3547 (1% in Diethylene Glycol Monomethyl Ether).

The two groups of rabbits sprayed for 1 and 5 seconds, respectively, displayed a slight skin redness and a slight conjunctivitis, both of which persisted for less than 15 minutes. No other signs of ocular or cutaneous irritation occurred during the 30-day observation period.

2. EA 3547 (1% in Propylene Glycol).

The two groups of six rabbits sprayed for 1 and 5 seconds, respectively, displayed a mild conjunctivitis for 15 minutes. One of the rabbits sprayed for 1 second developed a slight conjunctivitis the first day after exposure, which persisted for 1 day. No other signs of ocular or cutaneous irritation occurred during the 30-day observation period.

3. EA 3547 (1% in Dipropylene Glycol).

Both groups of rabbits displayed a slight conjunctivitis for up to 15 minutes. No other signs of ocular irritation occurred during the 30-day observation period.

4. CS (1% in Dipropylene Glycol).

The six rabbits sprayed for 1 second displayed an immediate conjunctivitis, which persisted for 12 to 48 hours. Two of the rabbits displayed a mild chemosis the first day after spraying, which persisted for 1 day. No other signs were seen in the subsequent 30-day observation period (table C-XI). The six rabbits sprayed for 5 seconds displayed an immediate redness, which persisted for 12 hours in five rabbits and 24 hours in one rabbit. No other signs were seen (table C-XI).

F. Intratracheal Toxicity Tests.

All dogs recovered uneventfully from anesthesia in 15 to 20 minutes and no abnormal signs or behavior were noted. No coughing, dyspnea, depression, anorexia, or weight loss occurred. Daily observations during the first week and semiweekly observations in the next 3 weeks revealed no abnormal clinical signs.

G. Inhalation Exposures.

Rats and guinea pigs, in groups of 22 per formulation, were exposed to pneumatically generated aerosols with the following Ct values (mg-min/cu m):

1% CS in dipropylene glycol, 1900
1% EA 3547 in propylene glycol, 2098
1% EA 3547 in dipropylene glycol, 2050

*The spray characteristics of the XM30 were tested against immobile targets in the field. The results are contained in appendix D.

Control animals in groups of 10 per solvent were exposed to dipropylene glycol and propylene glycol aerosols for 2 minutes. The only sign produced by the agent/solvent mixtures was marked ocular and nasal irritation which persisted for 1 hour after exposure. The control animals showed no signs during and after exposure to the solvents.

H. Pathology.

The only findings in the gross and microscopic examination of the approximately 400 animals necropsied were in the eyes of two monkeys and four rabbits that ocularly received 1% CS in dipropylene glycol for 5 days. These findings, however, are essentially negative (table C-XII). The changes observed in the monkeys are mild and certainly reversible. The changes seen in the rabbit eyes should not be related specifically to experimental procedures. These minor inflammatory lesions are seen routinely in rabbits that have never been in an experiment. The changes are probably related to a mild upper respiratory and related ocular infection with *Pasteurella multocida*.

IV. (U) SUMMARY AND CONCLUSIONS.

The results of the toxicological and pathological effects of the glycols and glycol ether in combination with CS and EA 3547 are essentially negative. The detailed evaluation of solutions of 1% CS in dipropylene glycol, 1% EA 3547 in propylene glycol, dipropylene glycol, and diethylene glycol monomethyl ether showed that all of the four meet the first six criteria listed in the Introduction of this report. In summary, they were demonstrated to cause no residual damage to the eyes, skin, or respiratory system on single or repeated applications; they have no systemic toxicity, indicating they do not penetrate the skin; they are stable at ambient and elevated temperatures; they undergo no marked changes in viscosity at low temperatures which would affect dissemination; they are all capable of being sprayed from the XM30 or similar hardware; and they are effective in producing local eye and skin irritation.

Based upon these findings, human testing to evaluate the last criterion—the formulation must be effective against motivated rioters—is indicated. The criteria specified in RL SOP 70-3 for determining the advisability of proceeding to respiratory testing in man have been met: none of the rodents exposed to aerosols of the formulations died (the glycol ether was not tested); no significant pathological changes were noted in gross and microscopic examination; all animals recovered completely except those rabbits receiving repeated ocular doses of CS (1% in dipropylene glycol).

(U) APPENDIXES

(C) APPENDIX A

TOXICITY OF SOLVENTS AND AGENTS (U)

I. (U) SOLVENTS.

A. Propylene Glycol.

The toxicity of propylene glycol has been reviewed by McNamara and Miller.[1] They stated that the LD50 values for single doses of this compound by various parenteral and oral routes of administration in different animal species are in the grams-per-kilogram range. Propylene glycol is less toxic than other glycols and many related compounds. Single inhalation exposures for 15 to 60 minutes at Ct's of 5,000 to 30,000 mg-min/cu m were nonlethal to mice.

Repeated parenteral and oral doses of propylene glycol in the grams-per-kilogram range have been well tolerated by human patients when administered as a solvent with therapeutic drugs. Rats and monkeys have inhaled propylene glycol in concentrations of 100 to 350 mg/cu m continuously for periods of 12 months. The exposures revealed little evidence of toxicity. In a study evaluating propylene glycol as an air disinfectant in a children's hospital, children inhaled concentrations of 48 to 94 mg/cu m of propylene glycol almost continuously for 3-week periods without signs of toxicity from the glycol.

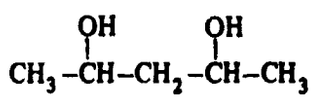
Propylene glycol is not damaging to the eyes of rabbits. It is generally not injurious to skin although there have been some skin reactions to prolonged contact in a covered patch test in patients attending a dermatological clinic.

B. Dipropylene Glycol.

Dipropylene glycol is prepared commercially as a byproduct of the manufacture of propylene glycol. It is used for many of the same purposes as the other glycols, but mostly in applications where its solubility characteristics (particularly with hydrocarbons) and lower volatility are useful. It is not used in drugs, pharmaceutical preparations, or food because its toxicological characteristics have not been clearly defined.

1. Physical and Chemical Properties.

Dipropylene glycol is a colorless, slightly viscous liquid with the formula



Its physical characteristics are as follows:

Molecular weight: 134.18
Specific gravity: 1.0252 (20/20°C); 1.026 (25/25°C)
Melting point: supercools
Boiling point: 231.9°C (760 mm Hg)
Vapor pressure: < 0.01 mm Hg (20°C)

Refractive index: 1.439 (25°C)
Percent in "saturated" air: < 0.0013 (20°C)
Solubility: soluble in water, methanol, and ether
Flash point: 250° to 280°F (open cup)
Conversion factors: 1 ppm = 5.49 mg/cu m at 25°C, 760 mm Hg; and 1 mg/l = 182 ppm at 25°C, 760 mm Hg

2. Effects in Animals.

a. Acute Toxicity Studies.

The intravenous LD50 of dipropylene glycol for dogs is 11.5 ml/kg.[2] Narcosis was produced in dogs by the intravenous injection of 5.9 ml/kg.[2]

The oral LD50 in the rat, reported by Hanzlik et al.,[2] is 14.8 gm/kg.

The intraperitoneal LD50 in the rat, reported by Hanzlik et al.,[2] is 10.3 ml/kg. The intraperitoneal LD50 in mice (Karel et al.[3]) is 4.39 ml/kg.

Carpenter et al.[4] report that when 0.5 ml of undiluted dipropylene glycol is applied to the rabbit eye, there is little or no irritation.

b. Chronic Toxicity Studies.

Rats were not affected by 5% dipropylene glycol in their drinking water for 77 days. Some of the animals that had been administered a level of 10% died with hydropic degeneration of kidney tubular epithelium and liver parenchyma. These effects were similar to those of diethylene glycol but less severe and less uniformly produced.[5]

In contrast to the increased activity produced by propylene glycol, depression of running activity occurred in rats given 12% dipropylene glycol in their diet for 15 weeks.[6]

The dogs examined by Hanzlik et al.[2] after repeated gastric dosing showed only moderate degenerative changes in the kidneys and only minimal evidence of liver damage.

When dipropylene glycol was applied repeatedly for prolonged periods (10 applications in 12 days) to the skin of rabbits, it had a negligible irritating action, and there was no indication that toxic quantities were absorbed through the intact skin.[7]

3. Effects in Man.

No untoward effects in man have been reported from the use of dipropylene glycol nor would any be expected because of the low systemic toxicity in animals and its low vapor pressure.[7]

4. Summary.

Although more acutely depressant to the central nervous system than are ethylene, diethylene, or propylene glycol, dipropylene glycol is still lower in oral toxicity to animals than

are the other glycols and is especially lower in liver toxicity. With repeated dosage, relatively large amounts of dipropylene glycol, as compared to diethylene glycol, are necessary before kidney damage occurs; and the damage is less severe than that caused by diethylene glycol. This compound is not irritating to the skin and is not absorbed in toxic amounts through the intact skin. No injurious effects on human beings have been recorded, and dipropylene glycol would appear to have practically no industrial hazard. Inhalation of its vapor would not be a problem because its vapor pressure is so low.

C. Diethylene Glycol Monomethyl Ether (Methyl Carbitol).

1. General.

Diethylene glycol monomethyl ether is a colorless liquid with a mild, pleasant odor and a bitter taste. Its industrial uses are similar to those of other glycol ethers, especially in the lacquer industry where it is used for thinners and quick-drying varnishes. While it is known that diethylene glycol monomethyl ether can be absorbed by the skin, no further information on its metabolic fate in the body is available.

2. Physical and Chemical Properties.

The formula of diethylene glycol monomethyl ether is

$$CH_3-O-CH_2-CH_2-O-CH_2-\underset{\displaystyle OH}{\underset{|}{CH_2}}$$

Its physical characteristics are as follows:

Molecular weight: 120.1
Boiling point: 194.2°C
Vapor pressure: 0.18 mm Hg at 25°C
Vapor density: 4.1 (air = 1)
Specific gravity (liquid density): 1.018
Flash point: 200°F
Conversion factors: 1 ppm = 4.91 mg/cu m; 1 mg/l = 204 ppm
Solubility: Miscible with water in all proportions

3. Effects in Animals.

a. Acute Toxicity Studies.

Smyth et al.[8] have reported the oral LD50 of a 50% aqueous solution in rats is 9.2 ml/kg of the undiluted material. Rowe[7] has reported that the LD50 for rats is 5.5 to 7 ml/kg. The LD50 of a 50% aqueous solution in guinea pigs is 4.16 gm/kg.[8]

Carpenter et al.[4] report that when applied to the rabbit eye, diethylene glycol monomethyl ether is painful but does not cause any permanent injury.

Studies using the "sleeve" technique* of Draize et al.[9] revealed that the percutaneous LD50 in rabbits is about 20 ml/kg.

Investigations by the Dow Chemical Company[7] in rabbits have shown that although this compound is not appreciably irritating to the skin, extensive and prolonged contact results in the absorption of toxic and even lethal amounts.

b. Chronic Toxicity Studies.

Repeated oral administration to rats of 1.83 gm/kg of diethylene glycol monomethyl ether over a long period has not proved lethal.[10]

One of a group of nine rats given drinking water containing 3% to 5% of diethylene glycol monomethyl ether for 11 to 64 days died on the 64th day.[5]

4. Effects in Man.

No injury to human beings, industrial or otherwise, has been reported.

5. Summary.

While generally recognized as being relatively low in toxicity to animals, this compound is regarded by some authorities[10] as being more toxic from the point of view of subacute poisoning than carbitol or butyl carbitol; Keston et al.[5] found its effects when administered over a brief period to be similar to those of carbitol and of diethylene glycol. It is not irritating to the skin; and though it can be absorbed by this route in toxic amounts, prolonged contact with a large amount is necessary.

Diethylene glycol monomethyl ether causes pain when applied to the eyes but does not cause any permanent injury. With a high oral dosage in animals, death occurs either through narcosis or kidney injury. Under normal conditions, hazard from inhalation is improbable because of its low volatility; but as no aminal experiments involving exposure to its vapor have been done, it can not be stated definitely that there is no possibility of hazard when this compound is heated or inhaled repeatedly.

II. (C) AGENTS.

A. (U) CS.

The toxicity of CS has been described by Weimer et al.[11]

B. (C) EA 3547.

1. (C) General.

During the synthesis of substituted dibenzoxazepine, the presence of an intensely irritating substance was noted by Dr. H. Suschitzky of the Royal Technical College, Salford.

*The agent is applied topically to the backs of clipped rabbits and the entire torso of the rabbit is covered with an impervious sleeve for 24 hours.

England. Subsequently, the highly irritating compound EA 3547 was found to be a sensory irritant of low toxicity and high activity.[1,2] As its effects were slightly longer lasting than those of CS, it seemed that it might meet the requirements of an improved riot control agent.

2. (U) Effects in Animals.

Most of the studies on the toxicity of EA 3547 are reported in the main body of this report. However, a few additional studies are discussed in the following paragraphs.

a. Ocular.

Doses of 0.1, 0.3, and 1.0 mg of EA 3547 in propylene glycol instilled in the eyes of rabbits produced irritation but no signs of damage lasting more than 2 days. No gross or microscopic pathological changes were noted when the animals were examined 30 days after ocular application.

b. Respiratory.

Animals were exposed to 2% EA 3547 in acetone as follows:

Rats and guinea pigs, 73,092 mg-min/cu m
Monkeys, 70,726 mg-min/cu m
Dogs, 57,171 mg-min/cu m

None of the animals died. The monkey showed no effects. Dogs, rats, and guinea pigs showed signs of nasal and ocular irritation immediately upon exposure, followed by hyperactivity, salivation, lacrimation, preening, vomiting, defecation (dogs), and bloody tears (guinea pigs).

3. (C) Effects in Man.

(C) The British[1,2] found that the proportion of men who were able to withstand the harassing atmosphere for 4 minutes indicated that EA 3547 was six times as active as CS. They also reported that there were only minor differences between the symptomatology of men exposed to EA 3547 and that of men exposed to CS; but skin irritation, especially on contact with water, continued with EA 3547 for some hours after exposure. This was not seen with CS.

III. (C) LITERATURE CITED.

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(U)

APPENDIX B

CHEMICAL STUDIES OF CS AND EA 3547 GLYCOL AND GLYCOL ETHER SOLUTIONS

I. PURPOSE.

The purpose of these studies was to determine the effect of temperature on the stability and viscosity of CS and EA 3547 solutions.

II. STABILITY STUDIES.

A. Test Solutions.

The following solutions were prepared.

1.0 gm CS in 100 ml propylene glycol
1.0 gm CS in 100 ml dipropylene glycol
1.0 gm CS in 100 ml diethylene glycol monomethyl ether
1.0 gm EA 3547 in 100 ml propylene glycol
1.0 gm EA 3547 in 100 ml dipropylene glycol
1.0 gm EA 3547 in 100 ml diethylene glycol monomethyl ether

B. Method of Preparing and Storing Solutions.

One-gram portions of each agent were transferred to 100-ml volumetric flasks and diluted with the appropriate solvent. Stirring was accomplished by means of a sonic bath at room temperature. All agents dissolved readily by this method except CS in propylene glycol. To effect solubilization of CS in this solvent, the temperature of the sonic bath was raised to 140°F and agitation was continued for 15 minutes. After all the agents were in solution, each sample was split into 50-ml portions and transferred to 125-ml Ehrlenmeyer flasks which were then stoppered. One portion was stored at 75°F and the other at 140°F.

C. Analytical Method and Procedure.

Both CS and EA 3547 absorb in the ultraviolet region. The absorption maximums found at 300 mμ for both CS and EA 3547 in ethanol were used for all solutions, with a quantitative range of 0.6 to 12 ppm and 1.5 to 32 ppm employed for CS and EA 3547 respectively. This method was found to be unworkable for the three solvents studied because dilute solutions of propylene glycol, dipropylene glycol, and diethylene glycol monomethyl ether are all transparent in the range of 220 to 400 mμ. When the 1% solution of an agent was diluted to 10 ppm with ethanol, the solvent fraction amounted to 0.1%, a quantity below the absorbance minimum. Ultraviolet scanning was made on the freshly prepared solution and periodically over the 30-day storage period. Degradation of the agent was determined directly from the amount of material quantitated from each scan by multiplying the slope factor (determined for each fresh solution) by the optical density.

D. Results.

The 30-day study of CS in propylene glycol was terminated after 1 week. By that time the 1% solution of CS stored at 140°F had almost completely degraded. Analysis revealed

that less than 1% of the CS remained. The solution stored at 75°F degraded by 25% over the same period, but because of the insolubility of the agent in this solvent, a large portion of the original 1% that had been solubilized by heating for 15 minutes at 140°F recrystallized from the solution. Because of these results, this solvent was eliminated from consideration as a carrier for CS in chemical spray weapons.

The solution of CS in diethylene glycol monomethyl ether was also unstable. After 8 days of storage at 140°F, only 26% of the agent remained. The solution stored at 75°F degraded at a slower rate, with 8% of the original CS still being active after 30 days. The degradation at 140°F, however, was sufficient reason to eliminate this solvent from consideration.

The solution containing 1% CS in dipropylene glycol was found to be essentially stable for a period of 30 days. The ultraviolet scans revealed no change in concentration of the CS solution stored at 75°F. The solution stored at 140°F degraded only about 10% after 30 days and darkened slightly. No wavelength shift was noticed in scans of either solution.

All solutions of EA 3547 stored at 75° or 140°F were stable for a period of 30 days. No physical changes were detected, nor were there any changes in the ultraviolet scan over the 30-day surveillance period.

The results of the ultraviolet analysis of the six solutions are shown in tables B-I and B-II. The ultraviolet scans of the six solutions are shown in figures B-1 through B-9.

III. VISCOSITY STUDIES.

A. Introduction.

The objective of these studies was to determine the effect of temperature on the viscosities of dipropylene glycol and propylene glycol as pure compounds and as solutions containing 1% CS and EA 3547. These data could then be utilized in assessing the spray capabilities of the solvent systems.

Two mathematically exact methods are available for measuring viscosity that do not require the use of standardizing liquids. The first is the capillary tube method formulated by Hagen.* The second is the method of the falling sphere, the laws of which were first formulated by Stokes.* The falling sphere method was selected for a number of reasons, the foremost being that it is applicable over a large range of viscosity (10^{-2} to 10^{14} centipoise); the equipment available can measure viscosity in the range from 0.5 to 200,000 centipoise; large amounts of material were available for measure; and no modifications of existing equipment were needed to complete the work.

The variation of the viscosity of many liquids with temperature is best expressed by means of an exponential or logarithmic equation:

$$N = Ae^{E/RT} \qquad (1)$$

*Bacon, L. R. The Measurement of Absolute Viscosity by the Falling Sphere Method. J. Franklin Ins. *221*, 251-252 (1936).

Table B-I (U) Stability of EA 3547 Solutions Stored at 75° and 140°F for 30 Days

Day	75°F		140°F	
	O.D.	% Remaining	O.D.	% Remaining
Dipropylene glycol (S.F. 34.24)				
1	0.292	100	0.292	100
7	0.284	97	0.292	100
14	0.298	102	0.298	102
16	0.292	100	0.292	100
22	0.307	105	0.298	102
31	0.301	103	0.296	101
Diethylene glycol monomethyl ether (S.F. 33.7)				
0	0.297	100	0.297	100
1	–	–	0.292	99
4	–	–	0.296	100
8	0.302	102	0.292	99
22	0.310	104	0.297	102
30	0.297	100	0.297	100
Propylene glycol (S.F. 34.7)*				
0	0.288	100		
3	0.284	98.5		
14	0.288	100		
23	0.288	100		
31	0.292	100		
Propylene glycol (S.F. 35.2)*				
0			0.284	100
1			0.284	100
7			0.285	100
11			0.286	100
21			0.288	100
30			0.284	100

*Two different solutions were made, accounting for the slightly different slope factors.

NOTE: O.D. = optical density; S.F. = slope factor.

Table B-II (U). Stability of CS in Solvent Systems Stored at 75° and 140°F for 30 Days

Day	75°F		140°F	
	O.D.	% Remaining	O.D.	% Remaining
Dipropylene glycol (S.F. 14.08)				
0	0.710	100	0.710	100
7	0.708	100	0.708	100
12	0.710	100	0.668	97
17	0.688	97	0.664	93
19	0.721	102	0.642	90
25	0.699	98	0.658	93
28	0.721	102	0.641	90
31	0.710	100	0.658	93
Propylene glycol (S.F. 12.77)				
0	0.783	100	0.783	100
4	0.678	87	0.347	44.3
7	0.585	75	0.143	18
Diethylene glycol monomethyl ether (S.F. 12.34)				
0	0.796	100	0.810	100
1	–	–	0.678	83
4	–	–	0.357	44
8	0.745	94	0.212	26
22	0.699	88	–	–
30	0.638	80	–	–

NOTE: O.D. = ocular density; S.F. = slope factor.

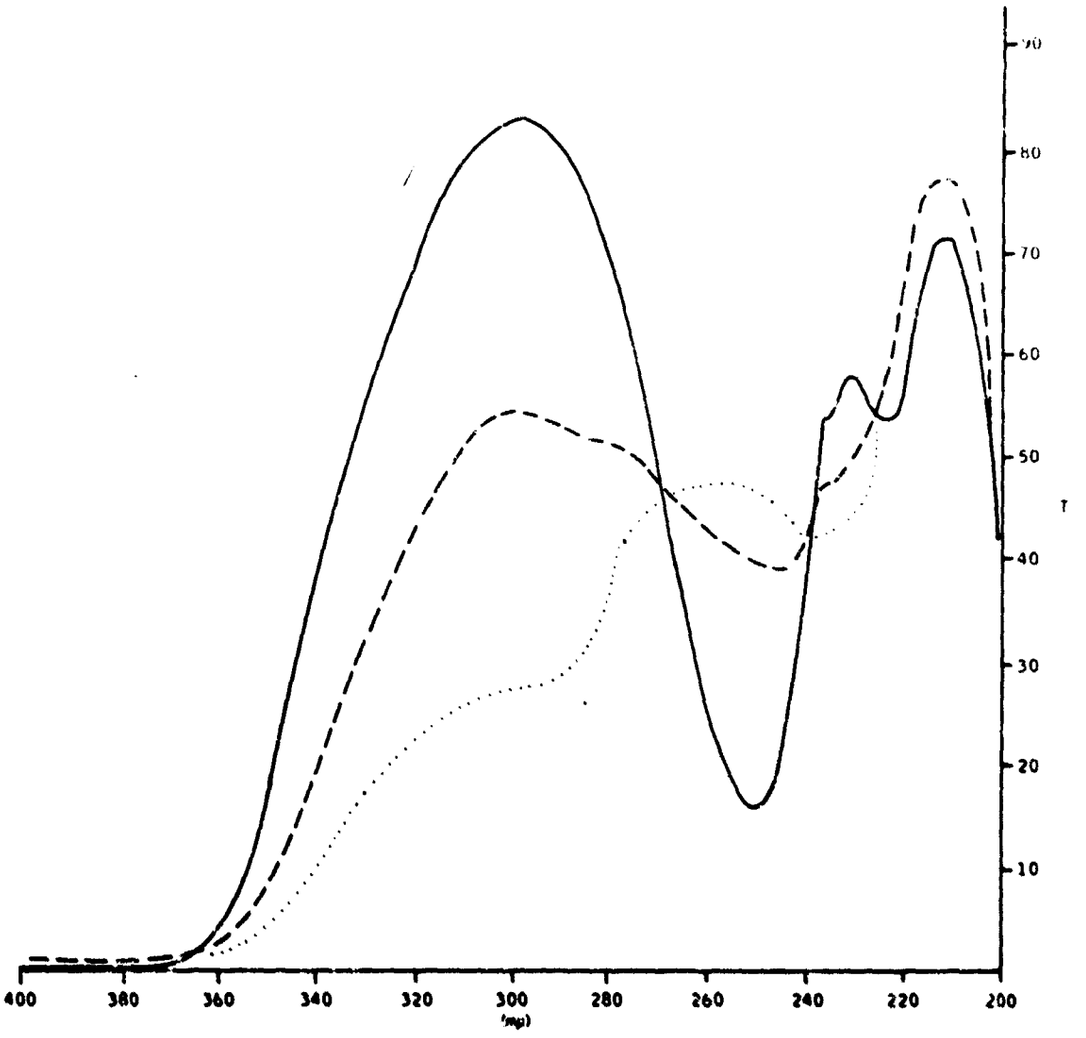

Figure B-1 (U). 1% CS in Propylene Glycol at 140°F
Legend: Initially ——— ; after 4 days - - - - ; after 7 days .....

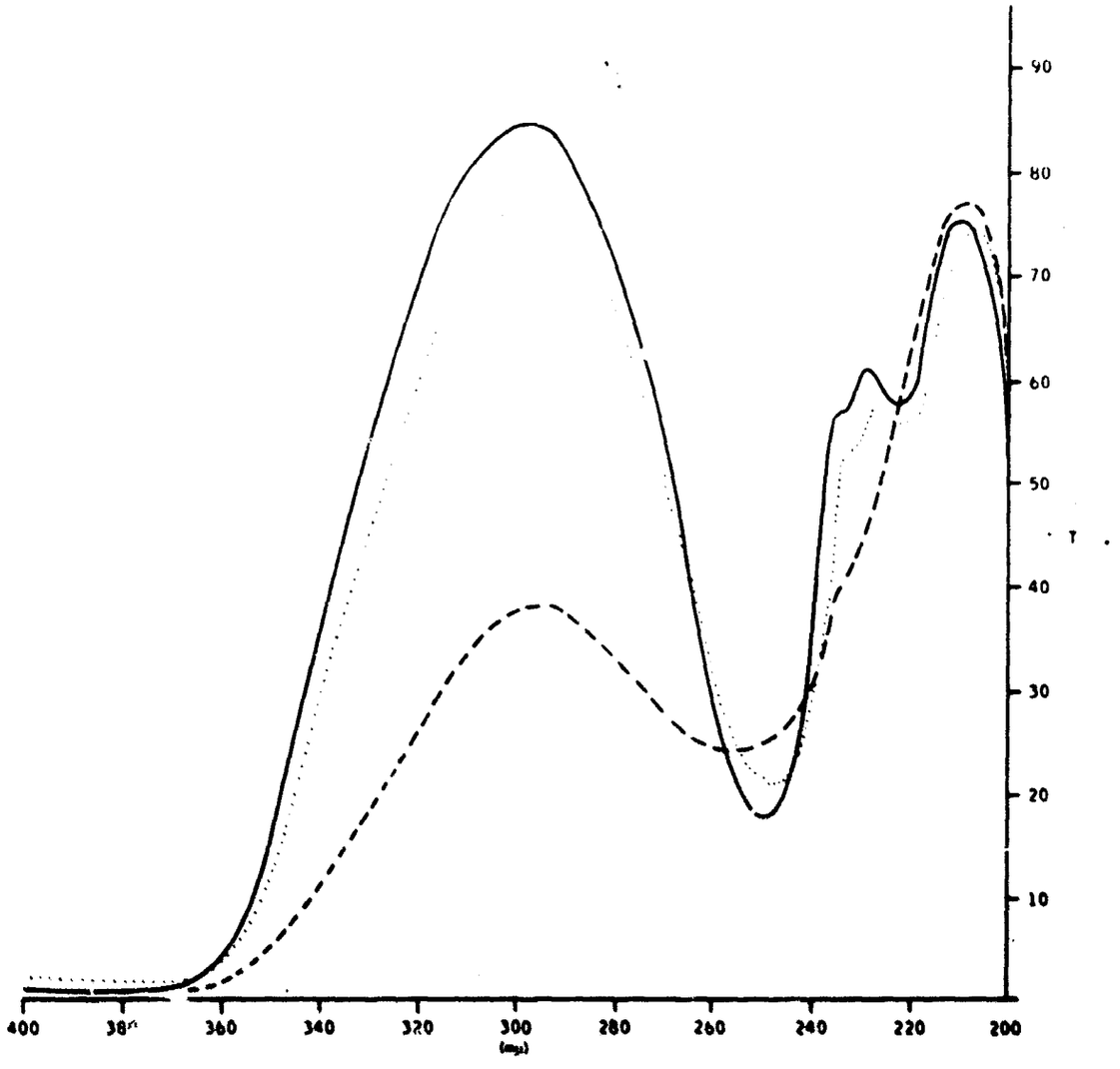

Figure B-2 (U). 1% CS in Diethylene Glycol Monomethyl Ether
Legend: Initially_____; after 30 days at 75°F _ _ _; after 30 days at 140°F.....

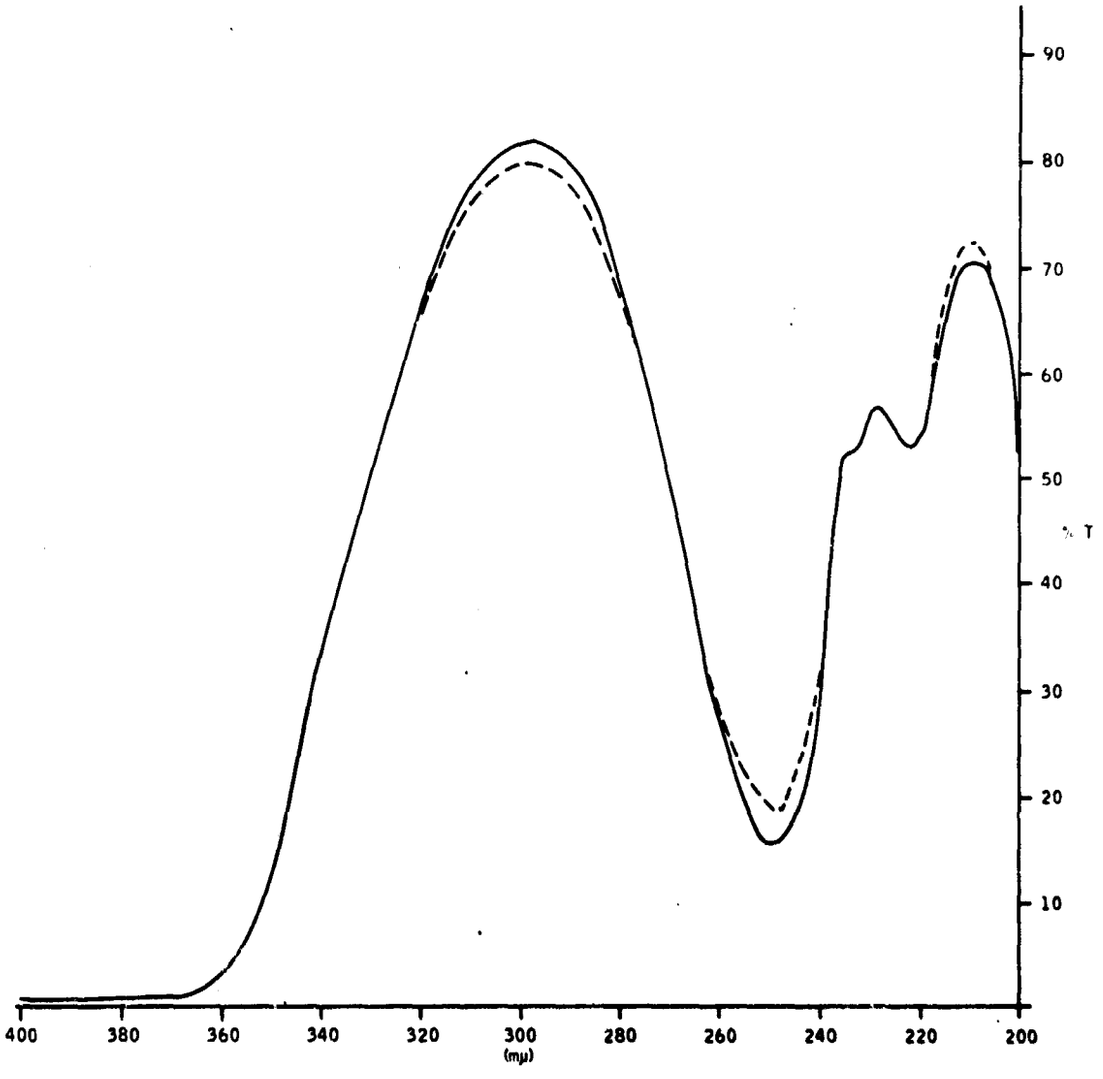

Figure B-3 (U). 1% CS in Dipropylene Glycol
Legend: Initially and after 30-day storage at 75°F_ _ _; after 30 days at 140°F_____

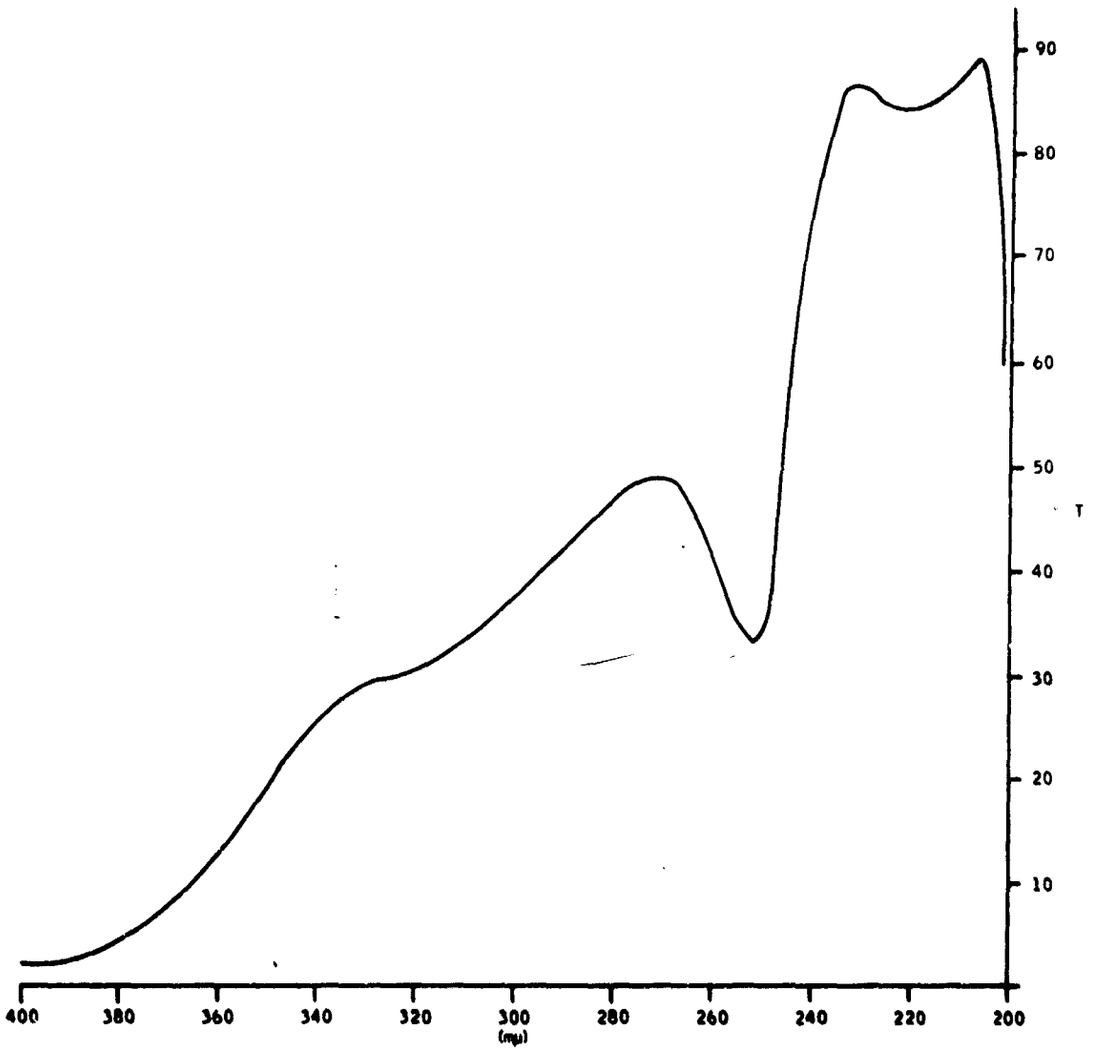

Figure B-4 (U). 1% EA 3547 in Dipropylene Glycol Initially

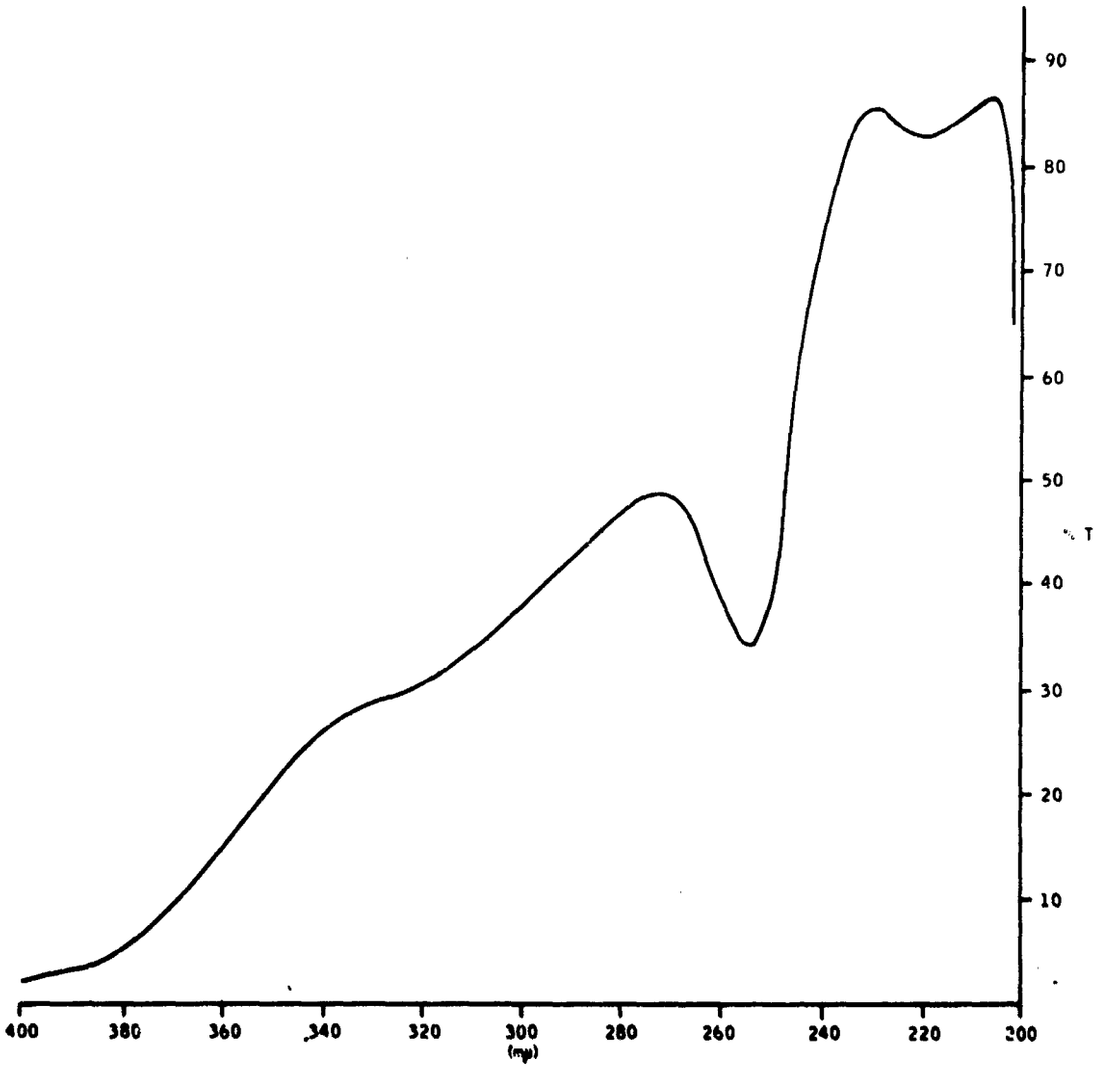

Figure B-5 (U). 1% EA 3547 in Dipropylene Glycol After 30 Days
Solutions stored at 75° and 140° F gave identical scans.

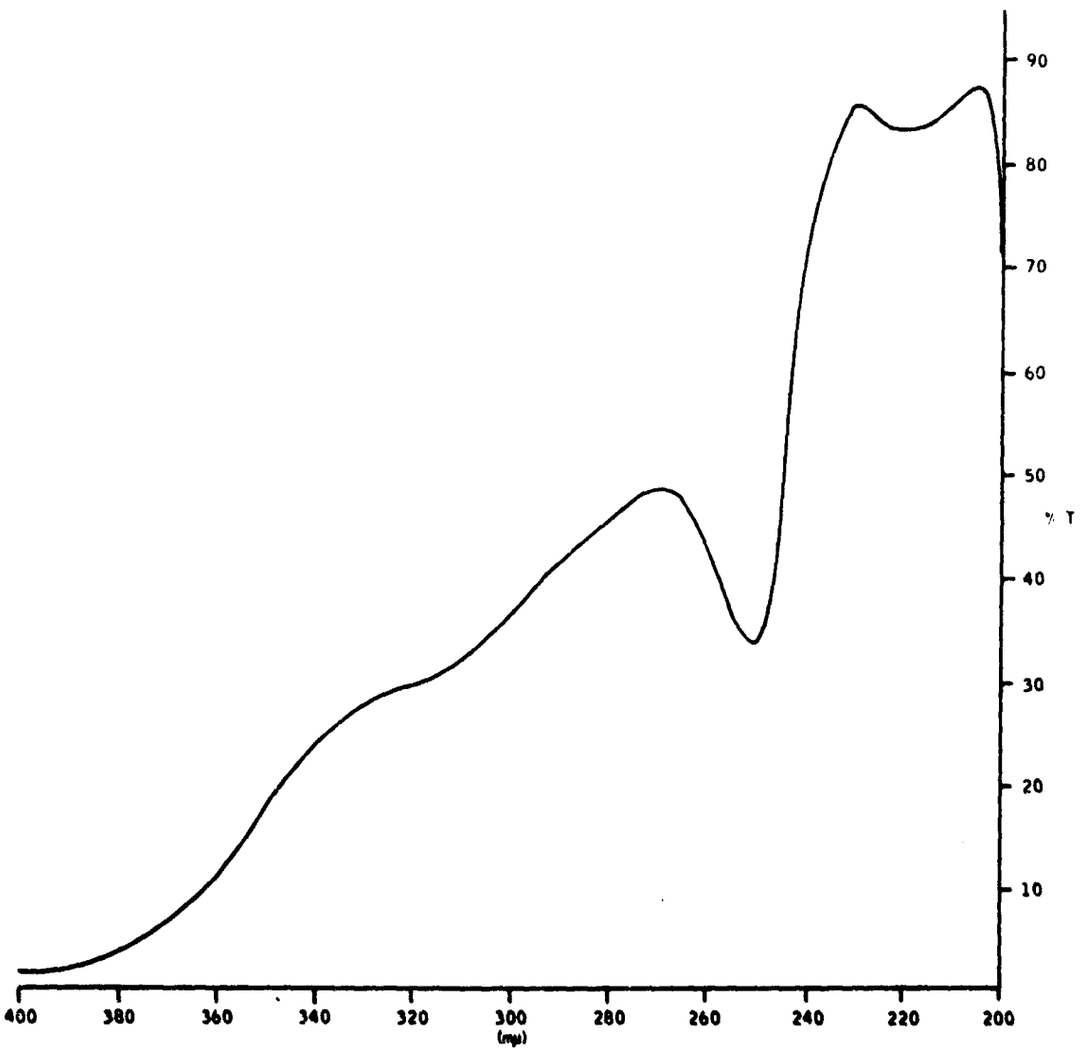

Figure B-6 (U). 1% EA 3547 in Propylene Glycol Initially

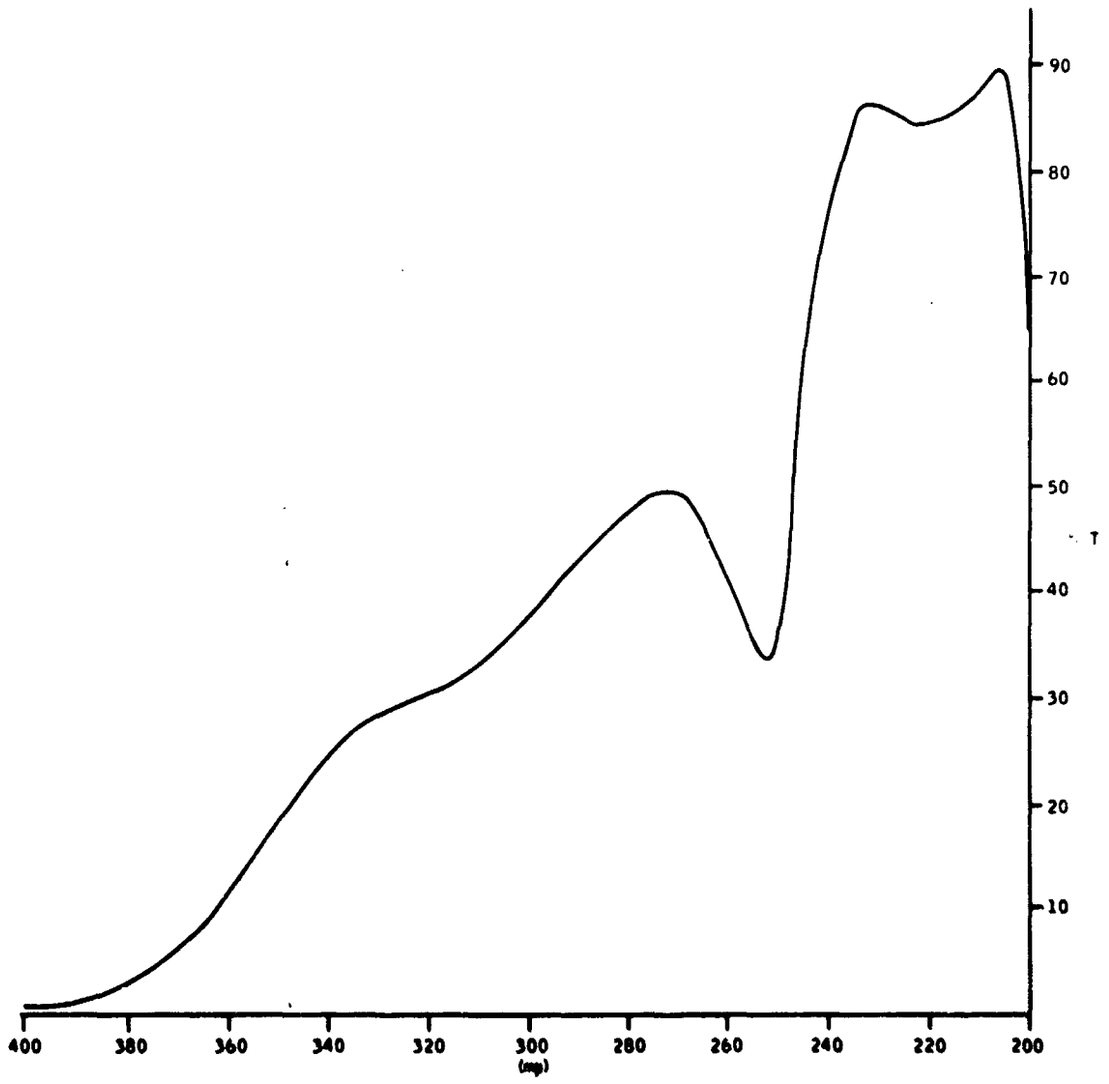

Figure B-7 (U). 1% EA 3547 in Propylene Glycol After 30 Days
Solutions stored at 75° and 140°F gave identical scans.

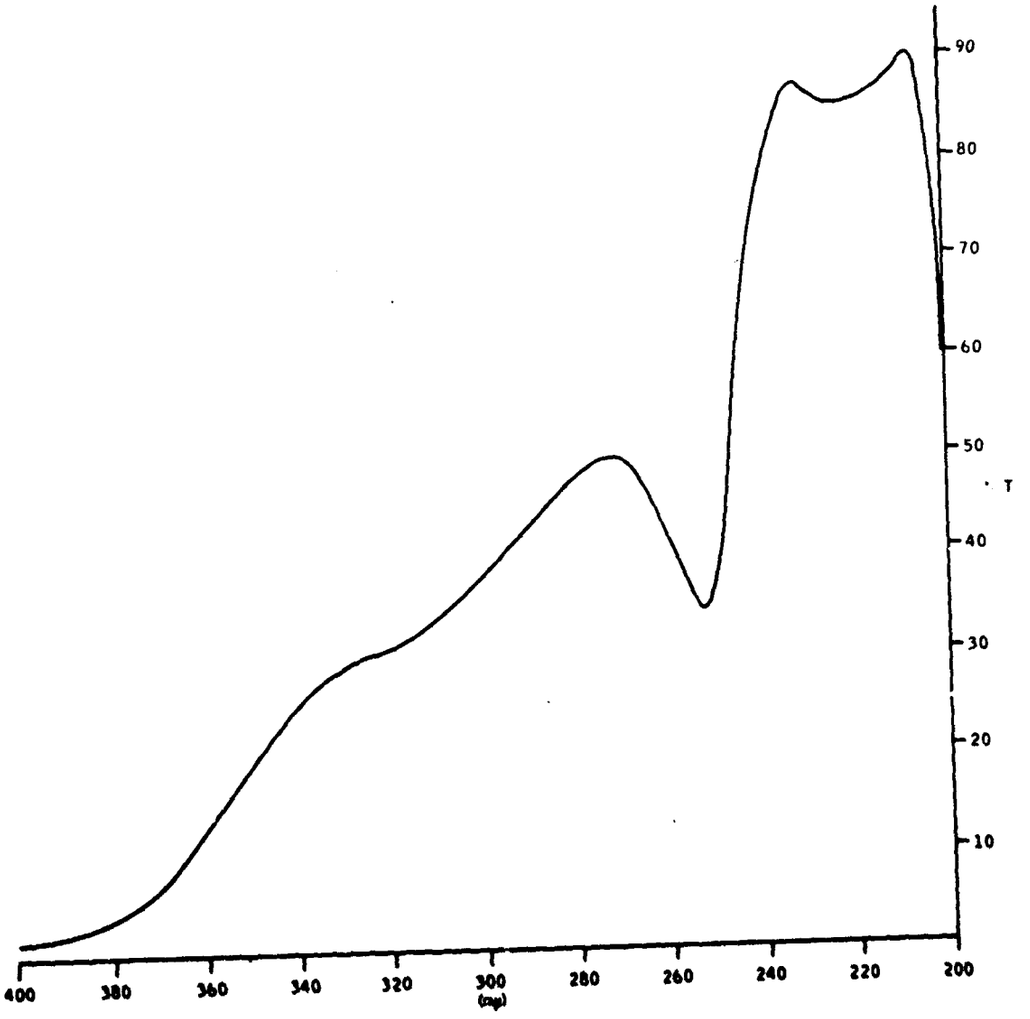

Figure B-8 (U). 1% EA 3547 in Diethylene Glycol Monomethyl Ether Initially

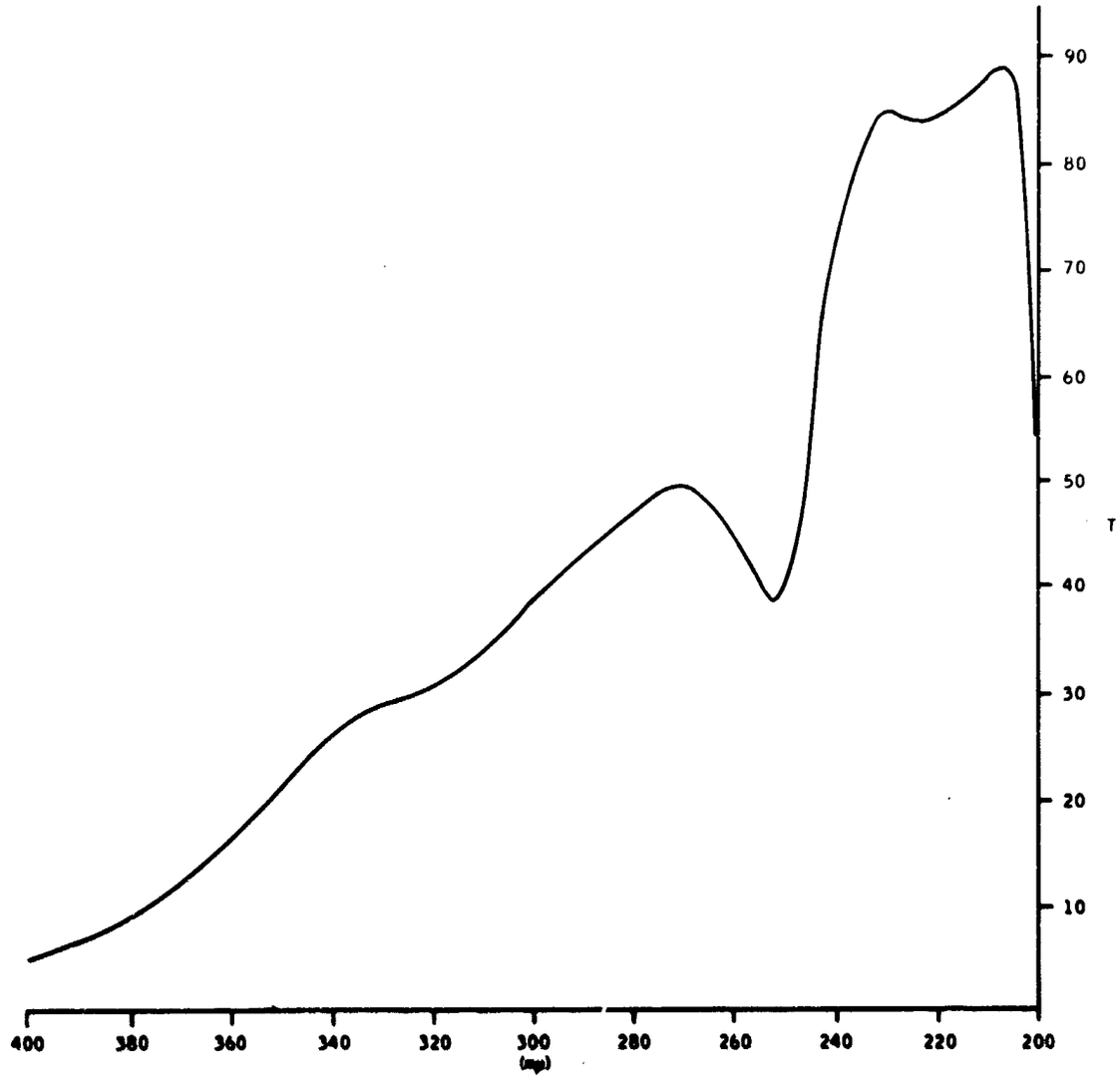

Figure B-9 (U). 1% EA 3547 in Diethylene Monomethyl Ether After 30 Days
Solutions stored at 75° and 140°F give identical scans.

or

$$\log N = (B/T) + C \tag{2}$$

where A and E, or B and C, are constants for the given liquid. According to equation (2) the plot of log N against the reciprocal of the absolute temperature $1/T$ should yield a straight line.*

B. Experimentation.

1. Equipment.

A Hoeppler precision viscometer, manufactured by Fish Schurman Corp., New Rockville, New York, was used for this study.

Temperature control was monitored with a circulating bath manufactured by the Precision Scientific Co., Chicago, Illinois (Catalog No. 66600).

2. Standardization and Calibration.

Three volumetric flasks were used and their volumes were determined directly from the weight of distilled water they would contain at known temperature. They were 99.8% to 99.9% of their nominal volume.

The densities of the various solutions and solvents as a function of temperature were determined by measuring the weight each would have when it would fill one of the volumetric flasks of known volume. A more elaborate technique was not necessary because the density correction is almost negligible.

Exactly 1.0000 gm of each compound was added to its respective solvent and made up to precisely 100 ml to give a 1.0000% (w/v) solution.

3. Calculation of Viscosity.

$$Cn = t\,(S_b - S_f)\,(B) \tag{3}$$

where

Cn = absolute viscosity in centipoise.
t = the time interval in seconds for fall of the ball through 100 mm.
S_b = density of the ball.
S_f = density of the fluid at the measuring temperature.
B = the ball constant which is experimentally determined.

Table B-III gives the values for S_b and B for three different ball types used in the viscosity studies. The ball falling times recorded for the pure solvents and for solvents containing either CS or EA 3547 at 32°, 76.6°, and 120.2°F are shown in tables B-IV, B-V, and B-VI. The viscosities of the five test materials, as calculated by (3) are shown in table B-VI.

*Glasstone, S. Elements of Physical Chemistry. 2d ed. Van Nostrand Company, New York, New York. 1960.

Table B-III (U). Ball Densities and Constants

Ball type	S_b	B	
		20°C	49°C
F6	2.2290	0.0755	0.0746
H8	7.9040	0.1336	0.1293
K10	7.8880	1.204	1.200

Table B-IV (U). Time for Fall of Ball Through 100 mm of Sample

Sample*	Ball	Falling time				Std dev
		Individual trials			Avg	
		sec				
Propylene glycol	H8	256.1	255.2	256.1	255.8	0.5
1% EA 3547 in propylene glycol	H8	244.0	241.8	242.6	242.8	1.1
Dipropylene glycol	K10	92.6	92.9	93.0	92.8	0.2
1% EA 3547 in dipropylene glycol	K10	87.2	87.7	87.4	87.4	0.25
1% CS in dipropylene glycol	K10	88.4	88.0	87.9	88.1	0.3

*Sample temp = 32°F (0°C).

Table B-V (U). Time for Fall of Ball Through 100 mm of Sample

Sample*	Ball	Falling time							Std dev
		Individual trials						Avg	
		sec							
Propylene glycol	H8	47.8	47.8	47.8	48.0	47.8	47.8	46.8	0.06
1% EA 3547 in propylene glycol	H8	46.8	46.6	46.7	46.8	46.6	46.7	46.7	0.09
Dipropylene glycol	H8	87.3 87.1	87.2	87.0	87.2	87.2	87.2	87.1	0.12
1% EA 3547 in dipropylene glycol	H8	86.2 86.2	86.0	86.2	86.0	86.0	86.0	86.1	0.11
1% CS in dipropylene glycol	H8	86.6 86.4	86.6	86.4	86.3	86.6	86.6	86.5	0.13

*Sample temp = 76.6°F (24.8°C).

Table B-VI (U). Time for Fall of Ball Through 100 mm of Sample

Sample*	Ball	Falling time						Std dev
		Individual trials					Avg	
		sec						
Propylene glycol	F6	146.6	146.2	146.4	146.4	146.5	146.4	0.15
1% EA 3547 in propylene glycol	F6	141.2	141.3	141.1	141.2	141.1	141.1	0.12
Dipropylene glycol	F6	202.4	202.0	202.4	202.4	202.2	202.3	0.18
1% EA 3547 in dipropylene glycol	F6	200.0	199.4	199.6	200.2	199.9	199.8	0.32
1% CS in dipropylene glycol	F6	198.0	197.6	198.4	197.8	198.2	198.0	0.32

*Sample temp = 120.2°F (49°C).

Table B-VII (U). Viscosity of Test Samples

Sample	Viscosity		
	32°F (0°C)	76.6°F (24.8°C)	120.2°F (49°C)
	centipoise		
Propylene glycol	234	43.9	13.3
1% EA 3547 in propylene glycol	222	42.9	12.8
Dipropylene glycol	765	80.1	18.6
1% EA 3547 in dipropylene glycol	720	79.2	18.2
1% CS in dipropylene glycol	726	79.2	18.2

C. (U) Results and Discussion.

A 1% EA 3547 solution in propylene or dipropylene glycol is slightly less viscous than the solvent alone. The same is true for a 1% CS solution in dipropylene glycol. The viscosity of 1% EA 3547 and 1% CS in dipropylene glycol is essentially the same within experimental error.

Figure B-10 relates the viscosity of the test materials to the reciprocal of the absolute temperature. The graph is linear through the range of 32° to 120°F and should be useful for obtaining reasonably accurate intermediate values. Work was not done below 32°F because temperature control is very critical at lower temperatures, but the graph should give an estimate of the viscosity at lower temperatures. The pour points of both propylene and dipropylene glycol are below - 50°F, and association effects would probably not be significant above - 10°F.

Because the graph of log *Cn* versus $1/T$ is linear, it is simple to arrive at an equation that may be preferable to reading off viscosity directly from the graph as a function of temperature. The method used for obtaining each equation is presented in figure B-11.

The final equations are:

Dipropylene glycol:

$$\log Cn = 5230\,(1/T - 0.001488)$$

1% CS and 1% EA 3547 in dipropylene glycol:

$$\log Cn = 5230\,(1/T - 0.001492)$$

Propylene glycol:

$$\log Cn = 4270\,(1/T - 001452)$$

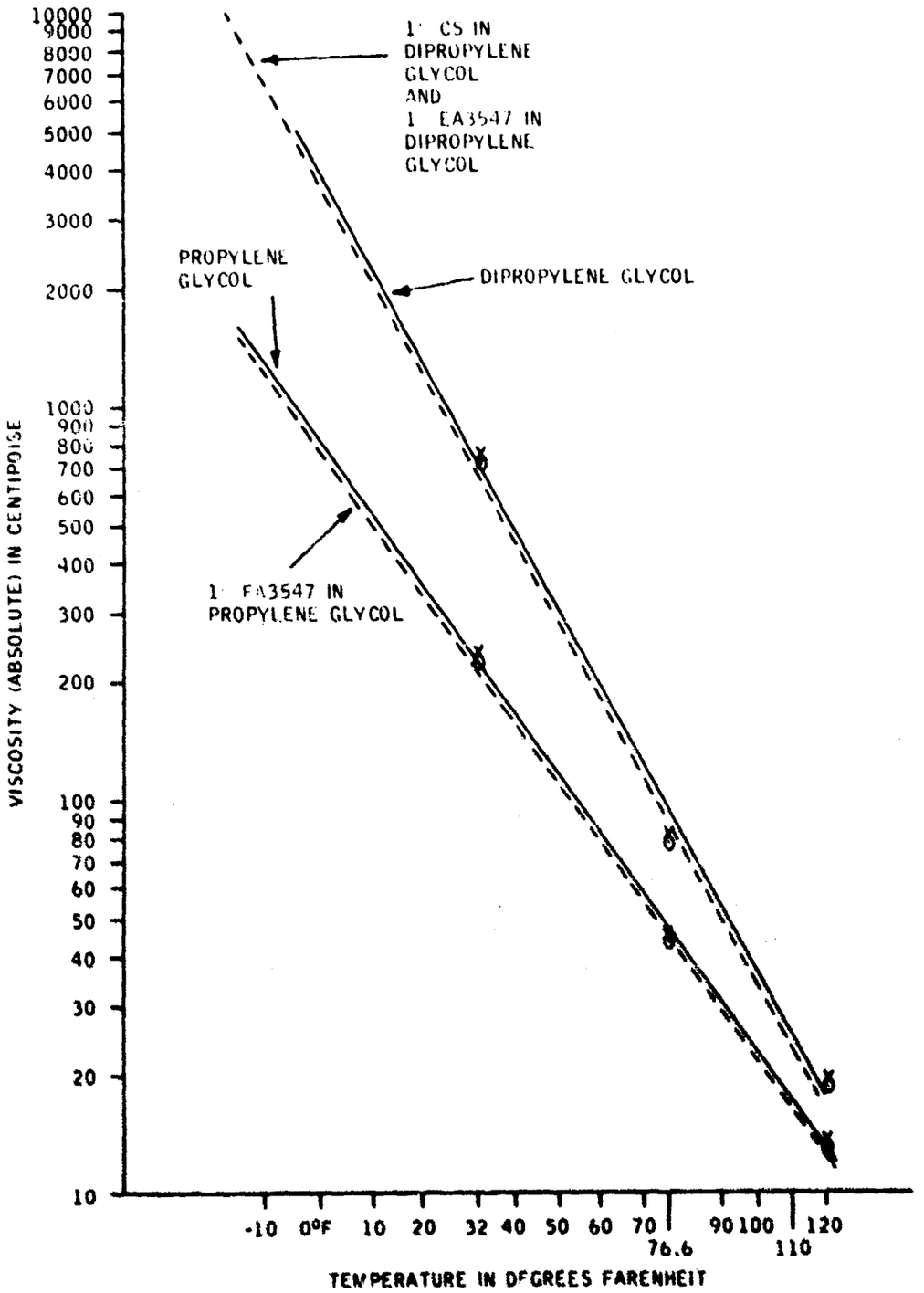

Figure B-10 (U). Viscosity of Test Materials Versus the Reciprocal of the Absolute Temperature

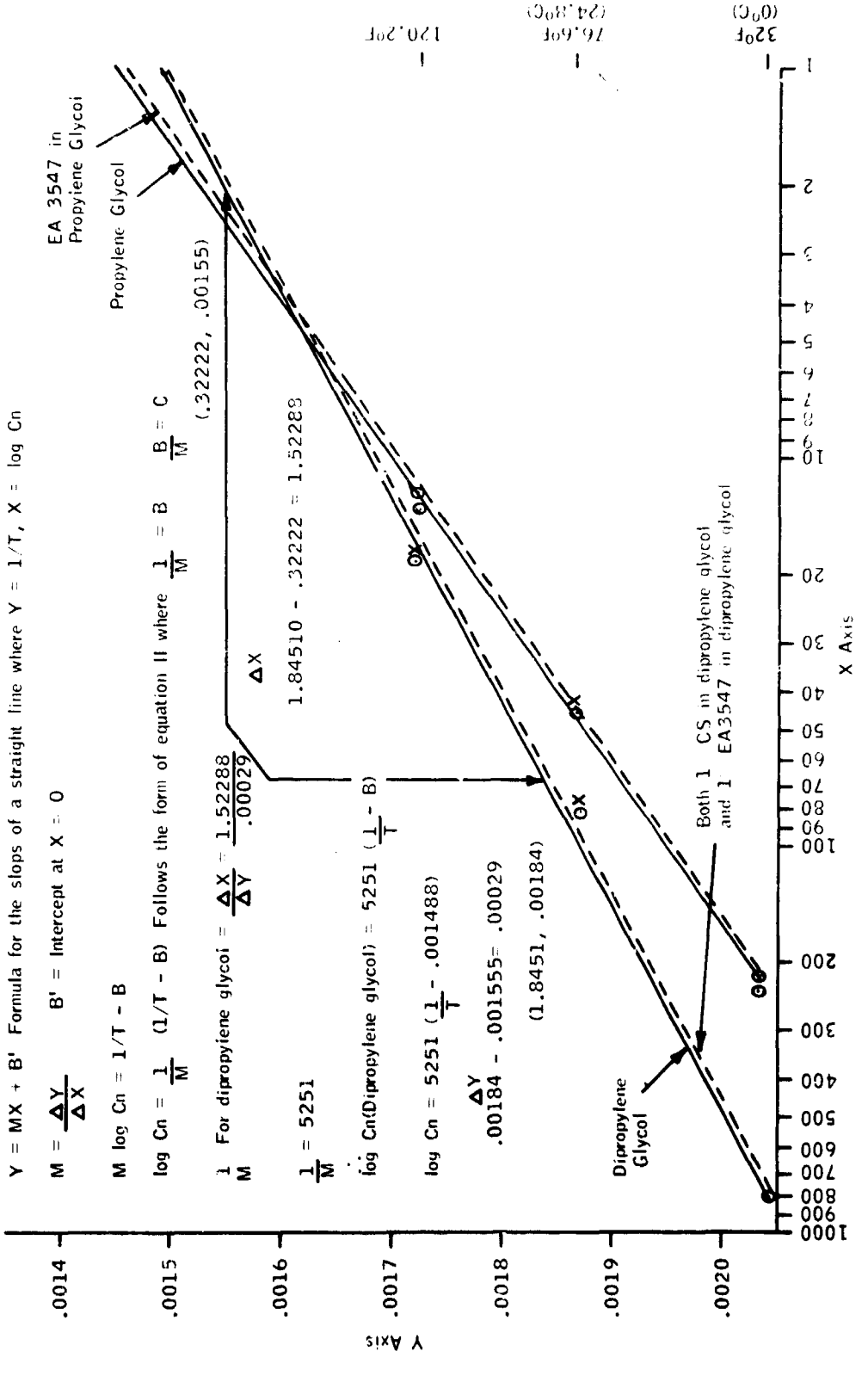

Figure B-11 (U). Viscosity of Test Materials at Elevated Temperature Versus the Reciprocal of the Absolute Temperature

1% EA 3547 in propylene glycol:

$$\log Cn = 4144\,(1/T - 0.001460)$$

where

Cn = viscosity in centipoise.
T = temperature in °F + 459.7 because the temperature must be expressed relative to absolute zero.

(U)

APPENDIX C

TOXICITY RESULTS

Table C-I (U). The Ocular Effects of CS (1% in Dipropylene Glycol) in Rabbits-- Single Dose

Dose	Animal No.	Gradation of effect after dosing															
		1 Day				2 Days				3 Days				4-30 Days			
		CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C
ml																	
0.2	13[a]	2	1	0	0	1	1	0	0	1	1	0	0				
0.2	14[a]	2	1	0	0	0	0	0	0	0	0	0	0				
0.2	15[b]	2	2	0	0	2	2	0	0	1	0	0	0	0	0	0	0
0.2	16[b]	2	1	0	0	1	1	0	0	1	1	0	0	0	0	0	0
0.2	17	2	1	0	0	2	1	0	0	2	1	0	0	0	0	0	0
0.2	18	2	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0

[a]Submitted for necropsy 3 days after dosing.

[b]Submitted for necropsy 30 days after dosing.

NOTE: CH = chemosis, R = redness, I = iritis, C = corneal involvement. Gradations are explained in table I.

Table C-II (U). The Cutaneous Effects of CS (1% in Dipropylene Glycol) in Rabbits Simple Dose

Dose	Animal No.	Gradation of effect after dosing											
		1 Day			2 Days			3 Days			4-30 Days		
		E	N	D	E	N	D	E	N	D	E	N	D
ml													
1.0	13[a]	1	0	0	1	0	0	1	0	0			
1.0	14[a]	0	0	0	0	0	0	0	0	0			
1.0	15[b]	1	0	0	1	0	0	1	0	0	0	0	0
1.0	16[b]	2	0	0	0	0	0	0	0	0	0	0	0
1.0	17	1	0	0	1	0	0	1	0	0	0	0	0
1.0	18	1	0	0	0	0	0	0	0	0	0	0	0

[a]Submitted for necropsy 3 days after dosing.

[b]Submitted for necropsy 30 days after dosing.

NOTE: E = erythema, N = necrosis, D = dehydration and/or desquamation. Gradations are explained in table II.

Table C-III (U). The Ocular Effects of Five Daily Doses of EA 3547 (1% in Diethylene Glycol Monomethyl Ether) in Rabbits

Dose	Animal No.	Gradation of effect (days after first dose)																					
		1 Day				2 Days				3 Days				4 Days				5 Days				6-30 Days			
		CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C
ml																									
0.2	31[a]	1	1	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	32[a]	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	33[b]	0	1	0	0	0	1	0	0	1	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0
0.2	34[b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	36	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 30 days after administration of last dose.

NOTE: CH = chemosis, R = redness, I = iritis, C = corneal involvement. Gradations explained in table I.

Table C-IV (U). The Cutaneous Effects of Five Daily Doses of EA 3547 (1% in Diethylene Glycol Monomethyl Ether) in Rabbits

Dose	Animal No.	Gradation of effect (days after first dose)																				
		1 Day			2 Days			3 Days			4 Days			5 Days			6 Days			7-35 Days		
		E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D
ml																						
1.0	31[a]	1	0	0	1	0	0	1	0	0	0	0	0	2	0	0	0	0	0	0	0	0
1.0	32[a]	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1.0	33[b]	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
1.0	34[b]	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0
1.0	35	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.0	36	1	0	0	0	0	0	0	0	0	1	0	0	2	0	0	1	0	0	0	0	0

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 30 days after administration of last dose.

NOTE: E = erythema, N = necrosis, D = dehydration and/or desquamation. Gradations are explained in table II.

Table C-V (U). The Cutaneous Effects of Five Daily Doses of EA 3547 (1% in Dipropylene Glycol) in Rabbits

Dose	Animal No.	Gradation of effect days after first dose																	
		1 Day			2 Days			3 Days			4 Days			5 Days			6-35 Days		
		E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D
ml																			
1.0	25[a]	1	0	0	2	0	0	0	0	0	0	0	0	1	0	0	0	0	0
1.0	26[a]	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
1.0	27[b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.0	28[b]	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0
1.0	29	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1.0	30	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
0.2	61[a]	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
0.2	62[a]	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	63[b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	64[b]	0	0	0	2	0	0	2	0	0	1	0	0	0	0	0	0	0	0
0.2	65	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0.2	66	0	0	0	1	0	0	0	0	0	1	0	0	0	0	0	0	0	0

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 30 days after administration of last dose.

NOTE: E = erythema, N = necrosis, D = dehydration and/or desquamation. Gradations are explained in table II.

Table C-VI (U). The Ocular Effects of Five Daily Doses of CS (1% in Dipropylene Glycol in Rabbits)

Dose	Animal No.	Gradation of effect (days after first dose)																											
		1 Day				2 Days				3 Days				4 Days				5 Days				6 Days				7 Days			
		CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C
ml																													
0.2	19[a]	0	1	2	0	1	1	2	0	2	1	2	0	4	2	0	3	4	3	0	4	4	2	0	3	4	2	0	3
0.2	20[a]	2	1	2	0	4	2	2	0	4	2	2	0	4	2	0	2	4	3	0	2	4	2	0	1	4	2	0	1
0.2	21	1	2	1	0	3	2	2	0	4	2	2	0	4	2	0	2	4	3	0	1	4	2	0	1	4	3	0	4
0.2	22	1	1	2	0	3	2	2	0	3	2	2	0	3	2	0	3	4	3	0	4	4	2	0	2	3	2	0	3
0.2	23	3	2	2	0	4	2	0	0	3	2	2	0	4	2	0	3	4	3	0	2	4	2	0	2	4	3	0	1
0.2	24	1	1	1	0	3	2	2	0	3	2	2	0	4	2	0	2	4	3	0	1	4	2	0	1	3	3	0	3
0.05	55[a]	0	1	0	0	2	0	1	0	3	2	2	0	1	2	0	1	1	2	0	1	0	1	0	0	0	0	0	0
0.05	56[a]	1	1	2	0	2	0	2	0	4	2	2	1	2	2	0	2	3	2	0	3	3	2	0	4	3	2	0	4
0.05	57	2	1	2	0	3	0	1	0	3	1	2	0	1	2	0	2	2	2	0	2	2	2	0	2	1	2	0	0
0.05	58	1	1	0	0	4	0	2	0	2	2	0	0	1	1	0	0	1	2	0	0	1	2	0	0	0	1	0	0
0.05	59	1	1	1	0	0	0	0	0	0	2	0	0	0	1	0	0	1	2	0	0	1	2	0	0	0	1	0	0
0.05	60	1	1	1	0	2	0	0	0	2	2	2	0	2	1	0	1	2	2	0	2	2	2	0	2	1	1	0	0

[a]Submitted for necropsy 3 days after administration of last dose.
NOTE: CH = chemosis, I = iritis, R = redness, C = corneal involvement. Gradations are explained in table I.

Table C-VI (U). Continued

Dose	Animal No.	Gradation of effect (days after first dose)																													
		8 Days				10 Days				10 Days				11 Days				12 Days				13 Days				14 Days					
		CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C		
ml																															
0.2	21	3	1	0	3	3	0	0	3	3	0	0	3	3	0	0	3	3	0	0	3	3	0	0	3	3	0	0	3		
0.2	22	3	0	0	3	3	0	0	2	3	0	0	2	3	0	0	2	3	0	0	2	3	0	0	2	3	0	0	2		
0.2	23	4	1	0	2	3	0	0	3	3	0	0	3	3	0	0	3	3	0	0	3	3	0	0	3	3	0	0	3		
0.2	24	3	2	0	4	3	1	0	2	2	0	0	2	2	0	0	2	2	0	0	0	2	0	0	2	2	0	0	2		
0.05	57	2	2	0	0	1	1	0	0	0	1	0	0	0	0	0	0	(11-30 days)													
0.05	58	0	2	0	0	0	1	0	0	0	0	0	0	0	(10-30 days)																
0.05	59	0	0	0	0	0	(8-30 days)																								
0.05	60	0	1	0	0	0	1	0	0	0	0	0	0	0	(10-30 days)																

Table C-VI (U). Continued

Dose	Animal No.	Gradation of effect[b] (days after first dose)																													
		15 Days				16 Days				17 Days				18 Days				19 Days				20 Days				21 Days				21-30 Days			
		CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C	CH	R	I	C
ml																															
0.2	21[c]	2	0	0	3	2	1	0	3	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2				
0.2	22[c]	2	2	0	2	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2				
0.2	23[d]	2	1	0	3	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2	2	1	0	2	0	0	0	2
0.2	24[d]	3	1	0	2	2	1	0	1	2	1	0	1	2	1	0	2	2	1	0	1	2	1	0	1	2	1	0	1	0	0	0	1

[b]The chemosis grading here is actually ptosis of the eyelid.

[c]Submitted for necropsy 21 days after administration of last dose.

[d]Submitted for necropsy 30 days after administration of last dose.

Table C-VII (U). The Cutaneous Effects of Five Daily Doses of CS (1% in Dipropylene Glycol) in Rabbits

Dose	Animal No.	Gradation of effect (days after first dose)																					
		1 Day			2 Days			3 Days			4 Days			5 Days			6 Days			7 Days			
		E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	
ml																							
1.0	19[a]	0	0	0	0	0	0	0	0	0	2	0	0	1	0	0	1	0	0	1	0	0	
1.0	20[a]	0	0	0	0	0	0	0	0	0	2	0	0	2	0	0	2	0	0	2	0	0	
1.0	21[b]	1	0	0	2	0	0	2	0	0	2	0	0	2	0	0	2	0	0	1	0	0	
1.0	22[b]	0	0	0	1	0	0	2	0	0	3	0	0	2	0	0	2	0	0	2	0	0	
1.0	23[c]	1	0	0	0	0	0	0	0	0	1	0	0	2	0	0	2	0	0	1	0	0	
1.0	24[c]	0	0	0	0	0	0	0	0	0	2	0	0	1	0	0	1	0	0	1	0	0	
0.2	55[a]	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	
0.2	56[a]	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	
0.2	57[b]	1	0	0	0	0	0	0	0	0	2	0	0	2	0	0	1	0	0	0	0	0	
0.2	58[b]	1	0	0	0	0	0	0	0	0	1	0	0	2	0	0	2	0	0	1	0	0	
0.2	59	1	0	0	0	0	0	0	0	0	0	0	0	2	0	0	1	0	0	0	0	0	
0.2	60	1	0	0	2	0	0	0	0	0	0	0	0	2	0	0	2	0	0	1	0	0	

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 21 days after administration of last dose.

[c]Submitted for necropsy 30 days after administration of last dose.

NOTE: E = erythema, N = necrosis, D = dehydration and/or desquamation. Gradations are explained in table II.

Table C-VII (U). Continued

Dose		Animal No.	Gradation of effect (days after first dose)																											
			8 Days			9 Days			10 Days			11 Days			12 Days			13 Days			14 Days			15 Days			16 Days			[illegible] days
			E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	L	N	D	L	N	D	L N D
ml																														
1.0		19	1	0	0																									
1.0		20	2	0	0																									
1.0		21	0	0	0	(8-26 days)						(10-26 days)																			
1.0		22	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0				
1.0		23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0				
1.0		24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0				
0.2		55	1	0	0																									
0.2		56	0	0	0																									
0.2		57	0	0	0	(8-30 days)																								
0.2		58	0	0	0	(8-30 days)																								
0.2		59	1	0	0	1	0	0	0	0	0	(10-30 days)																		
0.2		60	1	0	0	1	0	0	1	0	0	0	1	0	0	1	0	0	1	0	(14-30 days)									

Table C-VIII (U). The Ocular Effects of Five Daily Doses of CS (1% in Dipropylene Glycol) in Monkeys

Dose	Animal No.	Gradation of effect (days after first dose)																					
		1 Day			2 Days			3 Days			4 Days			5 Days			6 Days			7-35 Days			
		CH	R	C	CH	R	C	CH	R	C	CH	R	C	CH	R	C	CH	R	C	CH	R	C	
ml																							
0.2	771[a]	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	
0.2	747[a]	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	
0.2	749[b]	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	
0.2	765[b]	2	1	0	3	0	0	3	0	0	3	0	0	2	0	0	1	0	0	0	0	0	
0.2	746	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
0.2	758	0	0	0	0	2	0	0	2	0	0	2	0	0	2	0	0	0	0	0	0	0	
0.05	764[a]	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	
0.05	745[a]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
0.05	761	0	0	0	1	1	0	1	1	0	1	1	0	1	1	0	1	1	0	0	0	0	
0.05	762[b]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
0.05	748[b]	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	
0.05	744	0	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 30 days after administration of last dose.

NOTE: CH = chemosis, R = redness, C = corneal involvement. Gradations are explained in table I.

Table C-IX (U). The Cutaneous Effects of Five Daily Doses of EA 3547 (1% in Dipropylene Glycol) Applied to Sateen Patches Taped to the Clipped Backs of Rabbits

Dose	Animal No.	Gradation of effect after last dose											
		1 Day			2 Days			3 Days			4-30 Days		
		E	N	D	E	N	D	E	N	D	E	N	D
ml													
1.0	145[a]	0	0	0	0	0	0	0	0	0			
1.0	146[a]	1	0	0	0	0	0	0	0	0			
1.0	147[b]	1	0	0	0	0	0	0	0	0	0	0	0
1.0	148[b]	0	0	0	0	0	0	0	0	0	0	0	0
1.0	149	0	0	0	0	0	0	0	0	0	0	0	0
1.0	150	0	0	0	0	0	0	0	0	0	0	0	0
0.2	181[a]	0	0	0	0	0	0	0	0	0			
0.2	182[a]	0	0	0	2	0	0	0	0	0			
0.2	183[b]	2	0	0	0	0	0	0	0	0	0	0	0
0.2	184[b]	0	0	0	0	0	0	0	0	0	0	0	0
0.2	185	0	0	0	0	0	0	0	0	0	0	0	0
0.2	186	0	0	0	1	0	0	0	0	0	0	0	0

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 30 days after administration of last dose.

NOTE: E = erythema, *ni* = necrosis, D = dehydration and/or desquamation. Gradations are explained in table II.

Table C-X (U). The Cutaneous Effects of Five Daily Doses of CS (1% in Dipropylene Glycol) Applied to Sateen Patches Taped to the Clipped Backs of Rabbits

Dose	Animal No.	Gradation of effect after last dose																				
		1 Day			2 Days			3 Days			4 Days			5 Days			6 Days			7-30 Days		
		E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D
ml																						
1.0	139[a]	0	0	0	1	0	0	1	0	0												
1.0	140[a]	1	0	0	1	0	0	1	0	0												
1.0	141[b]	1	0	0	0	0	0	1	0	0	0	1	0	0	1	0	0	1	0	0	1	0
1.0	142[b]	2	0	0	1	0	0	2	0	0	0	1	0	0	1	0	0	1	0	0	1	0
1.0	143	1	0	0	1	0	0	0	0	0	0	1	0	0	1	0	0	0	0	(6-30 days)		
1.0	144	2	0	0	1	0	0	2	0	0	0	1	0	0	1	0	0	0	0	(6-30 days)		
0.2	175[a]	0	0	0	0	0	0	0	0	0												
0.2	176[a]	2	0	0	1	0	0	1	0	0												
0.2	177[b]	1	0	0	1	0	0	1	0	0	0	1	0	0	1	0	0	0	0	(6-30 days)		
0.2	178[b]	1	0	0	1	0	0	0	0	0	0	(3-30 days)										
0.2	179	1	0	0	0	0	0	0	0	0	0	(3-30 days)										
0.2	180	0	0	0	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	(6-30 days)		

[a]Submitted for necropsy 3 days after administration of last dose.

[b]Submitted for necropsy 30 days after administration of last dose.

NOTE: E = erythema, N = necrosis, D = dehydration and/or desquamation. Gradations are explained in table II.

Table C-X (U). Continued

Dose	Animal No.	Gradation of effect after last dose																					
		8 Days			9 Days			10 Days			11 Days			12 Days			13-30 Days						
		E	N	D	E	N	D	E	N	D	E	N	D	E	N	D	E	N	D				
ml																							
1.0	139																						
1.0	140																						
1.0	141	0	1	0	0	1	0	0	1	0	0	1	0	0	1	0	0	0	0				
1.0	142	0	1	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0				
1.0	143																						
1.0	144																						

Table C-XI (U). The Ocular Effects of CS (1% in Dipropylene Glycol) Sprayed From the XM30 Spray Device at the Right Eyes of Rabbits From a Distance of 5 Feet

Spray time	Animal No.	Gradation of effect after dosing											
		1 Day			2 Days			3 Days			4-30 Days		
		CH	R	C	CH	R	C	CH	R	C	CH	R	C
sec													
1	83[a]	0	0	0	0	0	0	0	0	0			
1	84[a]	0	1	0	0	0	0	0	0	0			
1	85[b]	1	2	0	0	1	0	0	0	0	0	0	0
1	86[b]	1	2	0	0	1	0	0	0	0	0	0	0
1	87	0	1	0	0	0	0	0	0	0	0	0	0
1	88	0	0	0	0	0	0	0	0	0	0	0	0
5	89[a]	0	0	0	0	0	0	0	0	0			
5	90[a]	0	1	0	0	0	0	0	0	0			
5	91[b]	0	0	0	0	0	0	0	0	0	0	0	0
5	92[b]	0	0	0	0	0	0	0	0	0	0	0	0
5	93	0	0	0	0	0	0	0	0	0	0	0	0
5	94	0	0	0	0	0	0	0	0	0	0	0	0

[a]Submitted for necropsy 3 days after dosing.

[b]Submitted for necropsy 30 days after dosing.

NOTE: CH = chemosis, R = redness, C = corneal involvement. Gradations are explained in table I.

Table C-XII (U). Necropsy Findings in Animals Exposed Both Ocularly and Cutaneously to 1% CS in Dipropylene Glycol (Five Daily Doses)

Daily dose		Species	Time of sacrifice	Number of animals		Findings
Ocular	Cutaneous			Controls*	Exptl	
ml			*days after exposure*			
0.05	0.2	Rabbits	3	2	2	None
			30	2	2	None
0.2	1.0	Rabbits	21	1		None
			30	1		None
			21		2	Gross: Focal clouding and vascularization of the cornea
			30		1	Micro: Blepharitis, conjunctivitis, and keratoconjunctivitis
			30		1	Mild conjunctivitis
0.05	0.2	Monkeys	3	2		None
			3		1	None
			3		1	Moderate, acute conjunctivitis
			30	2	2	None
0.2	1.0	Monkeys	3	2	1	None
			3		1	Mild, diffuse, acute conjunctivitis
			30	2	2	None

*Only the vehicle was applied.

(U) APPENDIX D

PILOT STUDIES OF THE SPRAY CHARACTERISTICS OF THE XM30 SPRAY DEVICE

I. EXPERIMENTATION.

Field tests were conducted to determine the spray characteristics of two XM30 units under normal operating conditions. The units were tested with water and propylene glycol under dry nitrogen pressure. The units were actuated for 2 or 5 seconds, and the times of the last one or two tests for each charge were lengthened until the cans were empty. The unit was weighed after each actuation to determine the amount sprayed. Maximum spray distance was also measured.

In a second test, one of the units was loaded with propylene glycol containing 1% EA 3547. The unit was sprayed at the face and shoulder areas of three silhouettes covered with polyethylene patches. The silhouettes were sprayed from distances of 5, 10, 15, and 25 feet. The EA 3547 was extracted from the polyethylene patches with ethanol and the quantity recovered was determined by ultraviolet absorption.

Ambient temperature during testing was 91°F and relative humidity was 42%. Each unit was fired in the same direction as the prevailing winds, which ranged from 2 to 5 mph.

II. RESULTS.

Results of these tests are shown in tables D-I and D-II. Total spraying time for the units ranged from 21 to 49 seconds. The maximum range of the units was 15 feet and diminished proportionately with propellant charge. Under the conditions cited, the propylene glycol appeared to spray as well as the water. A 2-second spray of EA 3547 (1% in propylene glycol) from distances of 5 to 15 feet impacted 2.8 to 9.4 mg of EA 3547 on silhouette targets.

Table D-I (U) Spray Testing of XM30 Device (2 to 5 mph Wind)

Unit contents	Spray type	Initial load	Spray time	Maximum spray distance	Total sprayed		Residue
		gm	*sec*	*ft*	*gm*	*gm/sec*	*gm*
Unit 1, water	Thick, narrow	1270	2	15	144	72	
			2	15	114	57	
			2	15	97	49	
			5	10	172	34	
			5	10	118	24	
			5	10	114	23	
			5	6	130	26	
			5	6	98	20	
			5	3	76	15	
			5	3	57	11	
			8	1	33	4	
			49		91%		117
Unit 2, water	Fine, wide	1290	2	15	225	112	
			2	15	197	99	
			2	10	180	90	
			5	10	335	67	
			5	10	276	55	
			5	10-0	74	15	
			21		99.8		3
Unit 1, propylene glycol	Fine, scattered	1312	2	15	117	59	
			2	15	93	47	
			2	12	91	46	
			5	10	150	30	
			5	7	112	22	
			5	5	83	17	
			10	2	113	11	
			15	1-0	81	5	
			46		64%		472
Unit 2, propylene glycol	Fine, full	1323	2	15	199	100	
			2	15	128	64	
			2	12	137	69	
			5	12	284	57	
			5	8	267	53	
			5	6	190	38	
			8	1-0	108	13	
			29		99.2%		10

Table D-II (U). Impaction Characteristics of EA 3547 (1% in Propylene Glycol) When Sprayed From the XM30 Device onto Silhouette Targets

[Spray was fine and scattered; initial load = 1300 gm]

Spray time	Distance from target	Total sprayed		Amount of EA 3547 impacted on targets			
				One	Two	Three	Avg
sec	*ft*	*gm*	*gm/sec*	*mg*			
2	15	250	125	6.3	8.3	2.8	5.8
2	25	170	85	Unable to reach target			
2	10	90	45	8.5	7.9	5.0	7.1
2	5	80	40	9.4	5.1	4.5	6.3

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13. ABSTRACT

(C) The studies described in this report were performed to assess the toxicities of o-chlorobenzylidene malononitrile (CS) and dibenz(b, f)-1, 4-oxazepine (EA 3547) in glycol ether solutions when administered to animals as follows: single and repeated doses in the eye, single and repeated doses on the skin, single and repeated doses applied to cloth on skin, single doses administered into the trachea, sprays of the solutions disseminated from the XM30, onto the eyes and skin, and inhalation of aerosols. The only residual damage seen when 1% CS in dipropylene glycol was applied to the skin and eyes of rabbits and monkeys occurred in the corneas of the rabbits that received the repeated doses. No residual damage was seen when 1% EA 3547 in dipropylene glycol and in propylene glycol was applied to the skin and eyes of rabbits and monkeys once or for five consecutive days. The same was true of 1% EA 3547 in diethylene glycol monomethyl ether in rabbits. When solutions of 1% CS in dipropylene glycol and 1% EA in dipropylene glycol, propylene glycol, or diethylene glycol monoethyl ether were administered intratracheally to dogs, no residual damage occurred. Rats and guinea pigs exposed to aerosols of 1% CS in dipropylene glycol, 1% EA 3547 in propylene glycol, and 1% EA 3547 in dipropylene glycol showed no residual pathological effects.

14. KEYWORDS

CS	Cutaneous toxicity	Dipropylene
EA 3547	Inhalation toxicity	Diethylene glycol monomethyl ether
Ocular toxicity	Intratracheal toxicity	XM30 dispenser

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